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(54) COMPOSES DE DIMERES DE NUCLEOSIDES ET LEURS USAGES THERAPEUTIQUES
(54) L-NUCLEOSIDE DIMER COMPOUNDS AND THERAPEUTIC USES

(57) L'invention porte sur des dimères de nucléosides dont l'un au moins des nucléosides comporte un sucre L, ainsi que sur des préparations pharmaceutiques les contenant.

(57) The invention relates to nucleoside dimers containing an L-sugar in at least one of the nucleosides and their pharmaceutical compositions.

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(54) Title: L-NUCLEOSIDE DIMER COMPOUNDS AND THERAPEUTIC USES

(57) Abstract

The invention relates to nucleoside dimers containing an L-sugar in at least one of the nucleosides and their pharmaceutical compositions.

L-NUCLEOSIDE DIMER COMPOUNDS AND THERAPEUTIC USES

Field of Invention

This invention relates to dinucleoside dimers and
intermediates or derivative thereof useful in the
5   synthesis of such dimers, processes for their
preparation, pharmaceutical compositions containing
such, and methods of using such compounds to treat
various diseases, particularly cancer in mammals. More
particularly it relates to L-deoxyribofuranosyl
10   nucleoside phosphodiester dimers where the sugar moiety
of at least one of the nucleosides has an
L-configuration.

Background of the Invention

Modified nucleoside analogs are an important class
15   of available antineoplastic and antiviral drugs.
Currently, there are no therapeutic compounds in use
that are based on dimers of these nucleoside analogs.
While dimers of the naturally occurring D-
deoxyribofuranosyl nucleosides are well known, dimers
20   in which one or both nucleosides are of the unnatural
L-configuration are much less known, and their use in
therapy of neoplastic and viral diseases is unknown.

In the synthesis of DNA-related oligomers, types
of nucleoside dimers are synthesized as part of the
25   overall process. These dimers usually include bases
from naturally occurring DNA or RNA sequences. There
is much known in the art about nucleoside monophosphate
dimers. Many of these compounds have been synthesized
and are available commercially. However, these dimers
30   are made from nucleosides containing a sugar moiety in
D-configuration.

Reese, C.B., Tetrahedron 14 (1978) 3143 describes
the synthesis of fully-protected dinucleoside
monophosphates by means of the phosphotriester
35   approach.

Littauer, U.Z., and Soreg, H. (1982) in The
Enzymes, Vol XV, Academic Press, NY, p. 517 is a

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standard reference which describes the enzymatic
synthesis of dinucleotides.

Heikkilö, J., Stridh, S., Öberg,, B. and
Chattopodhyaya, J., Acta Chem. Scand. B 39 (1985) 657-
5   669, provides an example of the methodology used in the
synthesis of a variety of ApG nucleoside phosphate
dimers. Included are references and methods for
synthesis of 3'→5' phosphates and 2'→5' phosphates by
solution phase chemistry.

10   Gait, M., "Oligonucleotide Synthesis", IRL Press,
Ltd., Oxford, England, 1984, is a general reference and
a useful overview for oligonucleotide synthesis. The
methods are applicable to synthesis of dimers, both by
solution phase and solid phase methods. Both
15   phosphitetriester and phosphotriester methods of
coupling nucleosides are described. The solid phase
method is useful for synthesizing dimers.

Gulyawa, V. and Holy, A., Coll. Czec. Chem. Commun
44 613 (1979), describe the enzymatic synthesis of a
20   series of dimers by reaction of 2',-3' cyclic phosphate
donors with ribonucleoside acceptors. The reaction was
catalyzed by non-specific RNases. The donors are
phosphorylated in the 5'-position, yielding the
following compounds: donor nucleoside-(3'→5') acceptor
25   nucleoside. Dimers were made with acceptors, β-
L-cytidine, β-L-adenosine, and 9(α-L-lyxofuranosyl)
adenine. Also, a large number of dimers with D-
nucleosides in the acceptor 5' - position were made.

Holy, A., Sorm, F., Collect. Czech. Chem. Commun.,
30   34, 3383 (1969), describe an enzymatic synthesis of β-
D-guanylyl-(3'→5')-β-L-adenosine and β-D-guanylyl-
(3'→5')-β-L-cytidine.

Schirmeister, H. and Pfleiderer, W., Helv. Chim.
Acta 77, 10 (1994), describe trimer synthesis and
35   intermediate dimers, all from β-D-nucleosides. They
used the phosphoramidite method which gave good yields.

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Thus, dimers with L-deoxyribofuranosyl moieties in
any position are new, as are dimers with
L-ribofuranosyl moieties bonded to the 3'-position of
the phosphate internucleotide bond.

5   Modified nucleoside analogues represent an
important class of compounds in the available arsenal
of antineoplastic and antiviral drugs. The anticancer
agents 5-fluorodeoxyuridine (floxuridine), cytarabine
and deoxycoformycin and the antiviral drugs

10   3'-azidodeoxythymidine (AZT), dideoxycytidine (ddC),
dideoxyinosine (ddI), acyclovir, 5-iododeoxyuridine
(idoxuridine) fludarabine phosphate and vidarabine
(adenine arabinoside/ara A) are representative of this
class of monomeric nucleoside-derived compounds which

15   are used therapeutically.
           More recently, "antisense" oligonucleotide
analogues with modified bases and/or phosphodiester
backbones have been actively pursued as antiviral and
antitumor agents. While no clinically approved drug

20   has yet emerged from this class of compounds, it
remains a very active field of research. Recently,
antipodal L-sugar-based nucleosides also have found
application as potent antiviral agents because they can
inhibit viral enzymes without affecting mammalian

25   enzymes, resulting in agents that have selective
antiviral activity without concomitant mammalian
cytotoxicity.
           Most naturally occurring nucleosides have the D-
configuration in the sugar moiety. While the chemical

30   properties of L-nucleosides are similar to those of
their β-D-enantiomers, they exhibit very different
biological profiles in mammalian cells and do not
interfere with the transport of normal D-nucleosides.
For example, β-L-uridine is not phosphorylated at the

35   5'-position by human prostate phosphotransferase, which
readily phosphorylates the enantiomeric β-D-uridine.
Apparently, L-nucleosides are not substrates for normal

human cell kinases, but they may be phosphorylated by
viral and cancer cell enzymes, allowing their use for
the design of selective antiviral and anticancer drugs.

5   Oligonucleotides based on L-nucleosides have been
studied previously. Octamers derived from α- and β-
L-thymidine were found resistant to fungal nucleases
and calf spleen phosphodiesterase, which readily
degrades the corresponding β-D-oligonucleotide.
Fujimory, et al, S. Fujimory, K. Shudo, Y. Hashimoto,
10   J. Am. Chem. Soc., 112, 7436, have shown that
enantiomeric poly-α-DNA recognizes complementary RNA
but not complementary DNA. This principle has been
used in the design of nuclease-resistant antisense
oligonucleotides for potential therapeutic
15   applications.

Thus, L-nucleoside-based compounds have potential
as drugs against neoplastic and viral diseases. While
L-sugar-derived nucleosides and their oligonucleotides
have been widely evaluated for such activities, little
20   is known regarding the biological activities of shorter
oligomers such as dimers obtained by L-nucleoside
substitution.

This invention comprises novel L-nucleoside-
derived therapeutic antitumor agents. Novel
25   L-nucleoside-derived dinucleoside monophosphates, based
on L-α-5-fluoro-2'-deoxyuridine showed a remarkably
high potency activity profile in in vitro anti-cancer
assays, with indications of unique mechanisms of
action, including inhibition of telomerase. Therefore,
30   the L-nucleosides can serve as building blocks for new
drugs with the special advantage of low toxicity.

SUMMARY OF THE INVENTION

An object of the present invention is the
provision of a dinucleoside dimer containing at least
35   one L-sugar.

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A further object of the present invention is a
method of treating neoplastic disease with a
dinucleoside dimer containing at least one L-sugar.

A further object of the present invention is a
5   provision of a pharmaceutical composition containing
dinucleoside dimers with at least one L-sugar.

Thus, in accomplishing the foregoing objects,
there is provided in accordance with one aspect of the
present invention a compound of the formulae:
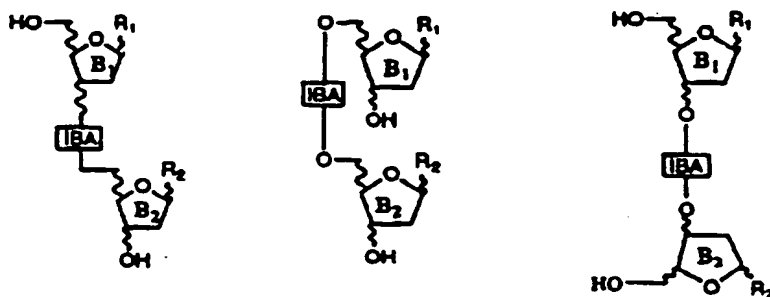
10   I   II   III

or a pharmaceutically acceptable salt thereof, wherein
A and B are each selected from the group consisting of
the β-D, β-L, and the α-L nucleosides and where in at
least one of A or B must be β-L or α-L nucleoside or α-
15   L or β-L furanose sugar, R_1 and R_2 are selected from
the group of bases consisting of cytosine, thymine,
uracil, adenine, guanine, or inosine, 5-fluorouridine
and other 5-halo uridines and wherein R_1 and R_2 can be
the same or a different base or alkoxy group such as
20   methoxy and wherein when A or B is attached to the
internucleotide binding agent (IBA) at the 5' position
and said A or B is β-L or α-L then the R_1 or R_2
attached to said A or B cannot be cytosine, and IBA is
selected from the group consisting of phosphodiester,
25   methoxy phospho-triesters, methylphosphonates,

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phosphorodithioates, phosphorothioates, silyl ethers, sulphonates and ethylenedioxy ethers.

    Specific compounds of the present invention which are effective include 3'-O-(α-L-5-fluoro-2'-deoxyuridinyl)-(3'→5')-β-D-5-fluoro-2'-deoxyuridine (L-102), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-α-L-5-fluoro-2'-deoxyuridine, (L-103), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-α-L-2'-deoxyuridine, (L-107), 3'-O-(α-L-5-fluoro-2'-deoxyuridinyl)-(3'→5')-α-L-5-fluoro-2'-deoxyuridine, (L-108), 3'-O-(α-L-5-fluoro-2'-deoxyuridinyl)-(3'→5')-β-L-5-fluoro-2'-deoxyuridine, (L-109), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-β-L-5-fluoro-2'-deoxyuridine, (L-110), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-α-L-2'-deoxycytidine, (L-111), 5'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(5'→5')-α-L-5-fluoro-2'-deoxyuridine (L-112), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-2'-deoxy-β-L-cytidine, (L-113), 3'-O-(2'-deoxy-β-L-cytidinyl)-(3'→5')-β-D-5-fluoro-2'-deoxyuridine (L-114), 3'-O-(2'-deoxy-α-L-cytidinyl)-(3'→5')-β-D-5-fluoro-2'-deoxyuridine (L-115), 3-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-β-L-2'-deoxyuridine (L-117), 3'-O-(β-L-2', 3'-dideoxy-cytidinyl)-(3'→5')-β-D-5-fluoro-2'-deoxyuridine (L-118), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-α-L-2', 3'-dideoxycytidine (L-120), 3'-O-(β-L-5-fluoro-2'-deoxyuridinyl)-(3'→5')-α-L-5-fluoro-2'-deoxyuridine (L-119), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→3')-α-L-5-fluoro-2'-deoxyuridine (L-122), 3'-O-(β-L-2'-deoxyuridinyl)-(3'→5')-β-D-5-fluoro-2'-deoxyuridine (L-124), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-α-L-2'-deoxyadenosine (L-125), 3'-O-(β-D-5-fluoro-2'-deoxyuridinly)-(3'→5')-α-L-thymidine (L-126), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-β-L-5-fluoro-2'-deoxyuridine phosphorothioate (L-128), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-β-L-2'-deoxyguanosine (L-133), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-α-L-2'-deoxyguanosine (L-134), 3'-O-(β-L-5-fluoro-2'-

deoxyuridinyl)-(3'→5')-methoxy-2-deoxyribose (L-136),
3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-α-L-2'-
deoxyadenosine (L-138) and 3'-O-(β-D-5-fluoro-2'-
deoxyuridinyl)-(3'→5')-β-L-1-methoxy-2-deoxyribose (L-
142).

5

More specifically, L-103, L-110 and L-117 are
found to be the preferred compounds.

Another embodiment of the present invention is a
pharmaceutical composition comprised of a pharma-
ceutically acceptable carrier and, a therapeutically
effective amount of at least one compound of the
present invention.

10

A further embodiment of the present invention is
the administration of a therapeutically effective
amount of the compounds of the present invention for
the treatment of cancer or viral infections.

15

Other and further objects, features and advantages
will be apparent from the following description of the
present preferred embodiments of the invention given
for the purposes of disclosure when taken in
conjunction with the accompanying drawings.

20

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic representation of the
dinucleotide dimers of the present invention.

Figures 2A, 2B and 3-8 are schematic
representations of the synthesis scheme followed in the
present invention. Figure 2A shows part of the
synthesis scheme for compounds of the present invention
(2'-deoxy-α-L-5-flouriuridene compound). Figure 2B
shows part of the synthesis scheme of compound N⁴-
benzoyl-2'-deoxy-α-L-cytidine, an intermediate in the
synthesis of the dimers.

25

30

Figure 3 shows the synthesis of a specific series
of alpha-beta or beta-alpha dimers.

Figure 4 shows the specific synthesis of an α-L-5
fluorouracil-β-D-5 fluorouracil.

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Figure 5 shows an alternate pathway for synthesis of dimer compounds.

Figure 6 shows an alternate pathway for synthesis of dimer compounds.

5 Figure 7A and 7B are a schematic representations of dinucleoside phosphate dimers containing alternate backbones including methoxyphosphotriesters and methyl phosphonates.

Figures 8A, 8B, 8C and 8D are schematic
10 representations of dinucleoside phosphate dimers used in the examples. Figure 8A shows a schematic representation of the dinucleotide dimers L-102, L-103, L-107 and L-109. Figure 8B shows a schematic representation of the dimers L-110, L-113, L-114 and
15 L-115. Figure 8C shows a schematic representation of dimers L-117, L-119 and L-112, Figure 8D shows a schematic representation of dimers L-115 and L-116.

The drawings that are not necessarily to scale, and certain features of the invention may be
20 exaggerated in scale or shown in schematic form in the interest of clarity and conciseness.

DETAILED DESCRIPTION

It is readily apparent to one skilled in the art that various substitutions and modifications may be
25 made to the invention disclosed herein without departing from the scope and spirit of the invention.

The term "dimers" as used herein is defined by the structures shown in Figure 1. These compounds are L-nucleoside-derived dinucleoside monophosphates. The
30 B_1 and B_2 units will consist of either a β-D, a β-L or an α-L nucleoside and at least one of B_1 or B_2 will be β-L or α-L. R_1 and R_2 will be the pyrimidine bases cytosine, thymine, uracil, or 5-fluorouridine (5-FUdR) other 5-halo compounds, or the purine bases, adenosine,
35 guanosine or inosine. As can be seen in Figure 1, the

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dimers can be bound either 5'-3', 3'-5', 3'-3', or
5'-5'.

Specific compounds of the present invention which
are effective include 3'-O-(α-L-5-fluoro-2'-
deoxyuridinyl)-(3'→5')-β-D-5-fluoro-2'-deoxyuridine (L-
102), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-α-L-
5-fluoro-2'-deoxyuridine, (L-103), 3'-O-(β-D-5-fluoro-
2'-deoxyuridinyl)-(3'→5')-α-L-2'-deoxyuridine, (L-107),
3'-O-(α-L-5-fluoro-2'-deoxyuridinyl)-(3'→5')-α-L-5-
fluoro-2'-deoxyuridine, (L-108), 3'-O-(α-L-5-fluoro-2'-
deoxyuridinyl)-(3'→5')-β-L-5-fluoro-2'-deoxyuridine,
(L-109), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-
β-L-5-fluoro-2'-deoxyuridine, (L-110), 3'-O-(β-D-5-
fluoro-2'-deoxyuridinyl)-(3'→5')-α-L-2'-deoxycytidine,
(L-111), 5'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(5'→5')-
α-L-5-fluoro-2'-deoxyuridine (L-112), 3'-O-(β-D-5-
fluoro-2'-deoxyuridinyl)-(3'→5')-2'-deoxy-β-L-cytidine,
(L-113), 3'-O-(2'-deoxy-β-L-cytidinyl)-(3'→5')-β-D-5-
fluoro-2'-deoxyuridine (L-114), 3'-O-(2'-deoxy-α-L-
cytidinyl)-(3'→5')-β-D-5-fluoro-2'-deoxyuridine (L-
115), 3-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-β-L-
2'-deoxyuridine (L-117), 3'-O-(β-L-2', 3'-dideoxy-
cytidinyl)-(3'→5')-β-D-5-fluoro-2'-deoxyuridine (L-
118), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-α-L-
2', 3'-dideoxycytidine (L-120), 3'-O-(β-L-5-fluoro-2'-
deoxyuridinyl)-(3'→5')-α-L-5-fluoro-2'-deoxyuridine (L-
119), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→3')-α-L-
5-fluoro-2'-deoxyuridine (L-122), 3'-O-(β-L-2'-
deoxyuridinyl)-(3'→5')-β-D-5-fluoro-2'-deoxyuridine (L-
124), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-α-L-
2'-deoxyadenosine (L-125), 3'-O-(β-D-5-fluoro-2'-
deoxyuridinly)-(3'→5')-α-L-thymidine (L-126), 3'-O-(β-
D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-β-L-5-fluoro-2'-
deoxyuridine phosphorothioate (L-128), 3'-O-(β-D-5-
fluoro-2'-deoxyuridinyl)-(3'→5')-β-L-2'-deoxyguanosine
(L-133), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-
α-L-2'-deoxyguanosine (L-134), 3'-O-(β-L-5-fluoro-2'-

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deoxyuridinyl)-(3'-5')-methoxy-2-deoxyribose (L-136),
3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'-5')-α-L-2'-
deoxyadenosine (L-138) and 3'-O-(β-D-5-fluoro-2'-
deoxyuridinyl)-(3'-5')-β-L-1-methoxy-2-deoxyribose (L-
5   142).

        The term "internucleotide binding agent" or "IBA"
means the backbone binding which links the nucleosides
together. Although one skilled in the art will readily
recognize a variety of other backbones are available
10   and useful in the present invention. For example, see
Figure 7, where methoxy phosphotriesters,
methylphosphonates and phosphorothioates are shown.
Although shown schematically 3'-5' the IBA's can be
used to link the sugars 5'-3', 3'-5', 3'-3', or 5'-5'.
15   In the preferred embodiment, the IBA of the compounds
is either phosphodiester or phosphorothioate.

        The term "antidisease" as used herein refers to
any of the activities of the compounds of the present
invention to affect a disease state, including
20   antitumor, antineoplastic, anticancer, antiparasitic
and antiviral activity.

        A compound or composition is said to be
"pharmacologically acceptable" if its administration
can be tolerated by a recipient mammal. Such an agent
25   is said to be administered in a "therapeutically
effective amount" if the amount administered is
physiologically significant. An agent is
physiologically significant if its presence results in
technical change in the physiology of a recipient
30   mammal. For example, in the treatment of cancer or
neoplastic disease, a compound which inhibits the tumor
growth or decreases the size of the tumor would be
therapeutically effective; whereas in the treatment of
a viral disease, a agent which slows the progression of
35   the disease or completely treats the disease, would be
considered therapeutically effective.

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Dosage and Formulation

     The antidisease compounds (active ingredients) of
this invention can be formulated and administered to
inhibit a variety of disease states (including tumors,

5   neoplasty, cancer, parasitic and viral diseases) by any
means that produces contact of the active ingredient
with the agent's site of action in the body of a
mammal. They can be administered by any conventional
means available for use in conjunction with

10   pharmaceuticals, either as individual therapeutic
active ingredients or in a combination of therapeutic
active ingredients. They can be administered alone,
but are generally administered with a pharmaceutical
carrier selected on the basis of the chosen route of

15   administration and standard pharmaceutical practice.
     The dosages given as examples herein are the
dosages usually used in treating tumors, neoplasty and
cancer. Dosages for antiparasitic and antiviral
applications will, in general be 10-50% of the dosages

20   for anticancer applications.
     The dosage administered will be a therapeutically
effective amount of active ingredient and will, of
course, vary depending upon known factors such as the
pharmacodynamic characteristics of the particular

25   active ingredient and its mode and route of
administration; age, sex, health and weight of the
recipient; nature and extent of symptoms; kind of
concurrent treatment, frequency of treatment and the
effect desired. Usually a daily dosage (therapeutic

30   effective amount) of active ingredient can be about 5
to 400 milligrams per kilogram of body weight.
Ordinarily, 10 to 200, and preferably 10 to 50,
milligram per kilogram per day given in divided doses 2
to 4 times a day or in sustained release form is

35   effective to obtain desired results.
     Dosage forms (compositions) suitable for internal
administration contain from about 1.0 to about 500

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milligrams of active ingredient per unit. In these
pharmaceutical compositions, the active ingredient will
ordinarily be present in an amount of about 0.05-95% by
weight based on the total weight of the composition.

5   The active ingredient can be administered orally
in solid dosage forms such as capsules, tablets and
powders, or in liquid dosage forms such as elixirs,
syrups, emulsions and suspensions. The active
ingredient can also be formulated for administration

10   parenterally by injection, rapid infusion,
nasopharyngeal absorption or dermoabsorption. The
agent may be administered intramuscularly,
intravenously, or as a suppository.

         Gelatin capsules contain the active ingredient and
15   powdered carriers such as lactose, sucrose, mannitol,
starch, cellulose derivatives, magnesium stearate,
stearic acid, and the like. Similar diluents can be
used to make compressed tablets. Both tablets and
capsules can be manufactured as sustained release

20   products to provide for continuous release of
medication over a period of hours. Compressed tablets
can be sugar coated or film coated to mask any
unpleasant taste and protect the tablet from the
atmosphere, or enteric coated for selective

25   disintegration in the gastrointestinal tract.

         Liquid dosage forms for oral administration can
contain coloring and flavoring to increase patient
acceptance.

         In general, water, a suitable oil, saline, aqueous
30   dextrose (glucose), and related sugar solutions and
glycols such as propylene glycol or polyethylene
glycols are suitable carriers for parenteral solutions.
Solutions for parenteral administration contain
preferably a water soluble salt of the active

35   ingredient, suitable stabilizing agents and, if
necessary, buffer substances. Antioxidizing agents
such as sodium bisulfate, sodium sulfite or ascorbic

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acid either alone or combined are suitable stabilizing
agents. Also used are citric acid and its salts and
sodium EDTA. In addition, parenteral solutions can
contain preservatives such as benzalkonium chloride,
5   methyl- or propyl-paraben and chlorobutanol. Suitable
pharmaceutical carriers are described in *Remington's
Pharmaceutical Sciences*, a standard reference text in
this field.

Additionally, standard pharmaceutical methods can
10   be employed to control the duration of action. These
are well known in the art and include control release
preparations and can include appropriate
macromolecules, for example polymers, polyesters,
polyaminoacids, polyvinyl, pyrolidone,
15   ethylenevinylacetate, methyl cellulose, carboxymethyl
cellulose or protamine sulfate. The concentration of
macromolecules as well as the methods of incorporation
can be adjusted in order to control release.
Additionally, the agent can be incorporated into
20   particles of polymeric materials such as polyesters,
polyaminoacids, hydrogels, poly (lactic acid) or
ethylenevinylacetate copolymers. In addition to being
incorporated, these agents can also be used to trap the
compound in microcapsules.

25   Useful pharmaceutical dosage forms for
administration of the compounds of this invention can
be illustrated as follows.

Capsules: Capsules are prepared by filling
standard two-piece hard gelatin capsulates each with
30   100 milligram of powdered active ingredient, 175
milligrams of lactose, 24 milligrams of talc and 6
milligrams magnesium stearate.

Soft Gelatin Capsules: A mixture of active
ingredient in soybean oil is prepared and injected by
35   means of a positive displacement pump into gelatin to
form soft gelatin capsules containing 100 milligrams of

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the active ingredient. The capsules are then washed
and dried.

Tablets: Tablets are prepared by conventional
procedures so that the dosage unit is 100 milligrams of
5   active ingredient. 0.2 milligrams of colloidal silicon
dioxide, 5 milligrams of magnesium stearate, 275
milligrams of microcrystalline cellulose, 11 milligrams
of cornstarch and 98.8 milligrams of lactose.
Appropriate coatings may be applied to increase
10   palatability or to delay absorption.

Injectable: A parenteral composition suitable for
administration by injection is prepared by stirring
1.5% by weight of active ingredients in 10% by volume
propylene glycol and water. The solution is made
15   isotonic with sodium chloride and sterilized.

Suspension: An aqueous suspension is prepared for
oral administration so that each 5 millimeters contain
100 milligrams of finely divided active ingredient, 200
milligrams of sodium carboxymethyl cellulose, 5
20   milligrams of sodium benzoate, 1.0 grams of sorbitol
solution U.S.P. and 0.025 millimeters of vanillin.

The dimers prepared for the studies described
herein are shown in Figures 1 and 6. Specific
combinations of the dimers are shown in Table 1.

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Table 1 - Structures of the Dinucleoside Monophosphate
         Dimers

Compound #	A	B
1	β-L-5FUdR	β-D-5UdR
2	β-L-5FUdR	α-L-5UdR
3	β-L-5FUdR	β-L-5FUdR
4	α-L-5UdR	α-L-5UdR
5	β-D-5FUdR	β-L-5FUdR
6	α-L-5UdR	β-L-5FUdR
7	α-L-dU	β-D-5FUdR
8	α-L-dC	β-D-5FUdR
9	α-L-dT	β-D-5FUdR
10	β-L-dU	β-D-5FUdR
11	β-L-dC	β-D-5FUdR
12	β-L-dT	β-D-5FUdR
13	α-L-5UdR	β-L-5FUdR
14	β-D-5FUdR	α-L-dC
15	α-L-5FUdR	β-D-5FUdR(3'-3')
16	β-D-5FUdR	β-L-dU
17	α-L-5FUdR	β-L-5FUdR
18	α-L-dG	β-D-5FUdR
19	β-L-dG	β-D-5FUdR
20	β-L-dA	β-D-5FUdR
21	β-D-1-OMe.dR	β-L-5FUdR
22	β-L-1-OMe.dR	β-D-5FUdR

The synthesis schemes in Figures 2 to 6 show the
general synthesis pathways for the dimers. Specific
synthesis pathways are more fully discussed in the
examples.

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A compound of the formulae:

    I   II   III
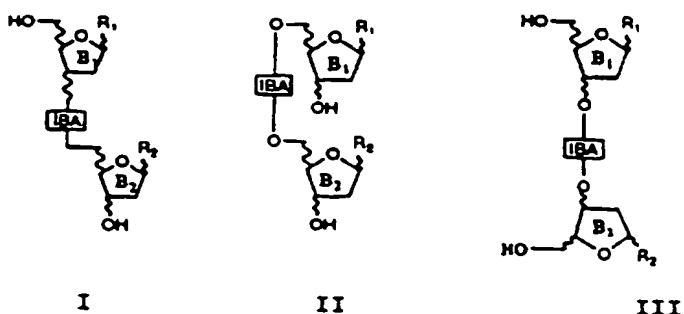
or a pharmaceutically acceptable salt thereof, wherein
B_1 and B_2 are each selected from the group consisting
of the β-D, β-L, and the α-L nucleosides and wherein at
least one of B_1 or B_2 must be β-L or α-L nucleoside, R_1
and R_2 are selected from the group of bases consisting
of cytosine (C), thymine (T), uracil (U), adenine (A),
guanosine (G), inosine (I), 5-fluorouridine (5FUdR) and
other 5-halo bases and wherein R_1 and R_2 can be the
same or a different base and wherein when B_1 or B_2 is
attached to the internucleotide binding agent (IBA) at
the 5' position and said B_1 or B_2 is β-L or α-L then
the R_1 or R_2 attached to said B_1 or B_2 cannot be
cytosine, and IBA is selected from the group consisting
of phosphodiester, methoxy phosphotriesters,
methylphosphonates and phosphorodithioates.

Specific compounds of the present invention which
are effective include 3'-O-(α-L-5-fluoro-2'-
deoxyuridinyl)-β-D-5-fluoro-2'-deoxyuridine, (L-102),
3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-α-L-5-fluoro-2'-
deoxyuridine, (L-103), 3'-O-(β-D-5-fluoro-2'-
deoxyuridinyl)-α-L-2'-deoxyuridine, (L-107), 3'-O-(α-L-
5-fluoro-2'-deoxyuridinyl)-α-L-5-fluoro-2'-
deoxyuridine, (L-108), 3'-O-(β-L-5-fluoro-2'-
deoxyuridinyl)-β-L-5-fluoro-2'-deoxyuridine, (L-109),
3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-β-L-5-fluoro-2'-
deoxyuridine, (L-110), 3'-O-(β-D-5-fluoro-2'-
deoxyuridinyl)-α-L-2'-deoxycytidine, (L-111), 3'-O-(β-

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D-5-fluoro-2'-deoxyuridinyl)-2'-deoxy-β-L-cytidine (L-
113), 3'-O-(2'-deoxy-β-L-cytidinyl)-β-D-5-fluoro-2'-
deoxyuridine (L-114), 3'-O-(2'-deoxy-α-L-cytidinyl)-β-
D-5-fluoro-2'-deoxyuridine (L-115), 3'-O-(β-D-5-fluoro-
5   2'-deoxyuridinyl)-β-L-2'-deoxyuridine (L-117), 3'-O-(β-
L-5-fluoro-2'-deoxyuridinyl)-α-L-5-fluoro-2'-
deoxyuridine (L-119), 3'-O-(β-D-5-fluoro-2'-
deoxyuridinyl)-α-L-5-fluoro-2'-deoxyuridine (3', 3')
(L-122).

10   More specifically, L-103, L-110 and L-117 are
found to be the preferred compounds.
           Another embodiment of the present invention is a
pharmaceutical composition comprised of a pharma-
ceutically acceptable carrier and, a therapeutically
15   effective amount of at least one compound of the
present invention.
           A further embodiment of the present invention is
the administration of a therapeutically effective
amount of the compounds of the present invention for
20   the treatment of cancer or viral infections.
           The following examples are offered by way of
illustration and are not intended to limit the
invention in any manner. The synthetic nucleosides and
dimers described in the examples can include any of the
25   substitutions discussed earlier. The backbone and base
modifying groups can be added. The substitutions will
enhance its affinity, the chemical stability and the
cellular uptake properties of the specific dimers
treatments.

30   Example 1
                Synthesis of 2'-deoxy-α-L-5-fluorouridine
           While β-D-5-fluoro-deoxyuridine is commercially
available, the α-L-isomer 2'-deoxy-α-L-5-flourouridine
is not, and this component of the dimers was
35   synthesized from L-arabinose.

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1-(2', 3', 5'-Tri-O-benzoyl-α-L-arabinofuranosyl)-5-
fluorouracil (3)

To a mixture of 5-fluorouracil (4.01 g, 30.87
mmol) and compound 2 (15.57 g, 30.87 mmol) in anhydrous
MeCN were successively added HMDS (5.20 ml, 24.69
mmol), ClSiMe₃ (3.10 ml, 24.69 mmol), and SnCl₄ (4.30
ml, 37.04 mmol). The resulting clear solution was
refluxed for one hour. Then the solvent was evaporated
and the residue was dissolved in EtOAc (750 ml), washed
with H₂O, and saturated NaHCO₃ solution. The EtOAc
layer was dried over sodium sulfate, filtered and
evaporated to give the crude product. This crude
product was purified on a silica gel column using 40-
50% EtOAc/petroleum ether to give pure 3 (11.7 g, 66.0%
yield) as a white foam.

NMR: (CDCl₃) δ = 4.65 (dd, 1H), 4.78 (dd, 1H), 4.97
(dd, 1H), 5.75-5.88 (2 t, 2H), 6.27 (d, 1H), 7.36-7.62
and 8.00-8.10 (m, 5H), 8.94 (d, 1H).

1-α-L-Arabinofuranosyl-5-fluorouracil (4)

To a solution of compound 3 (11.7 g, 20.37 mmol)
in MeOH (300 ml), NaOMe (4.2 ml of a methanolic 25% w/v
solution) was added and the solution was stirred until
the reaction was complete. The solvent was then
evaporated and the residue was dissolved in H₂O (200
ml), washed with ether and neutralized with Dowex 50
ion exchange resin. After filtration of the resin, the
aqueous solution was evaporated to give compound 4
(4.92 g, 92% yield) as a white foam.

NMR: (DMSO-d₆) δ = 3.48 (m, 2H), 3.93-4.00 (2 t, 2H),
4.16 (q, 1H), 5.69 (dd, 1H), 8.03 (d, 1H).

1-[3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-
α-L-Arabinofuranosyl]-5-fluorouracil (5)

To a stirred suspension of 4 (6.43 g, 24.52 mmol)
in pyridine (200 ml) was added 1,3-dichloro-1,1,3,3-
tetraisopropyldisiloxane (10.3 ml, 29.43 mmol). This
was stirred at room temperature until the reaction was
complete (5 hours). The solvent was evaporated to a

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residue which was dissolved in EtOAC and washed
successively with H_2O, 5% HCl, H_2O, saturated $NaHCO_3$,
and brine. After drying the EtOAc portion over Na_2SO_4,
the solution was filtered and evaporated to give the
5   crude product 5 which was used in the next step without
further purification.

1-[2'-O-phenoxythiocarbonyl-3',5'-O-(1,1,3,3-
tetraisopropyldisiloxane-1,3-diyl)-α-
L-arabinofuranosyl]-5-fluorouracil (6)

10   To a solution of 5 (24.52 mmol) in anhydrous MeCN
(300 ml) were added 4-dimethylaminopyridine (DMAP)
(5.80 g, 47.58 mmol), and phenylchlorethionoformate
(3.85 ml, 26.98 mmol). The solution was stirred at
room temperature for 24 hours. Then, the solvent was
15   evaporated to a residue which was dissolved in EtOAc
and washed successively with H_2O, 5% HCl, H_2O,
saturated $NaHCO_3$, and brine. After drying the EtOAc
portion over Na_2SO_4, the solution was filtered and
evaporated to an oil. The oil was purified on a silica
20   gel column using 30% EtOAc/petroleum ether to produce
pure 6 (8.9 g, 56.7% yield) as a yellow foam.
NMR: ($CDCl_3$) δ = 4.02 (m, 2H), 4.32 (m, 1H), 4.76 (dd,
1H), 6.10 (dd, 1H), 6.18 (dd, 1H), 7.07 -7.48 (m, 6H),
8.41 (br s, 1H).

25   3',5'-O-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-α-
L-2'-deoxy-5-fluorouridine (7)

        To a solution of 6 (8.92 g, 13.91 mmol), in dry
toluene (300 ml) was added AIBN (0.46 g, 2.78 mmol)
followed by Bu_3SnH (20.0 ml, 69.35 mmol). The solution
30   was deoxygenated with argon and heated at 75°C for four
hours. The solvent was then evaporated and the residue
was purified on a silica gel column using 30%
EtOAc/petroleum ether to give pure 7 (5.44 g, 80%
yield) as a white foam.
35   NMR: ($CDCl_3$) δ = 2.16 (m, 1H), 2.84 (m, 1H), 3.79 (m,
1H), 4.07 (m, 1H), 4.60 (m, 1H), 6.19 (ddd, 1H), 7.92
(m, 1H).

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2'-Deoxy-α-L-5-fluorouridine (8)

A solution of compound 7 (5.44 g, 11.13 mmol) and
NH₄F (4.12 g, 111.3 mmol) in MeOH was stirred in an oil
bath at 60°C for 3 hours. Silica gel (3 g) was added

5   and the mixture was evaporated to a dry powder. This
powder was added to a silica column and eluted with 10-
15% MeOH/CHCl₃ to produce pure 8 (2.4 g, 87.6% yield)
as a white foam.

NMR: (DMSO-d₆) δ = 1.90 (m, 1H), 2.55 (m, 1H), 3.33

10   (m, 2H), 4.19 (m, 2H), 4.86 (br s, 1H), 5.43 (br s,
1H), 6.10 (dd, 1H), 8.15 (d, 1H), 11.78 (br s, 1H).

Example 2
Synthesis of 2'-deoxy-α-L-uridine
1-(2', 3', 5'-Tri-O-benzoyl-α-L-arabinofuranosyl)

15   uracil (9)

To a mixture of uracil (7.06g, 62.98 mmol) and
compound 2 (31.7 g, 62.98 mmol) in anhydrous MeCN were
successively added HMDS (10.6 ml, 50.38 mmol), ClSiMe₃
(6.4 ml, 50.38 mmol), and SnCl₄ (8.8 ml, 75.5 mmol).

20   The resulting clear solution was refluxed for one hour.
Then the solvent was evaporated and the residue was
dissolved in EtOAc (1.21 ml), washed with H₂O, and
saturated NaHCO₃ solution. The EtOAc layer was dried
over NA₂SO₄, filtered and evaporated to give the crude

25   product. This crude product was purified on a silica
gel column 50% using EtOAc/petroleum ether to give pure
2 (20.2 g, 57.7% yield) as a white foam.

NMR: (CDCl₃) δ = 4.65 (m, 2H), 4.95 (m, 1H), 5.79 (dd,
1H), 5.94 (t, 1H), 6.20 (d, 1H), 7.35-7.63 (m, 10H),

30   7.98-8.10 (m, 6H), 8.58 (br s, 1H).

1-α-L-Arabinofuranosyl-uracil (10)

To a solution of compound 8 (17.83 g, 32.03 mmol)
in MeOH (400 ml), NaOMe (5.0 ml of a methanolic 25% v/v
solution) was added and the solution was stirred until

35   the reaction was complete. The solvent was then
evaporated and the residue was dissolved in H₂O (250

ml), washed with ether and neutralized with Dowex 50
ion exchange resin. After filtration of the resin, the
aqueous solution was evaporated to give compound 10
(7.4 g, 94.6% yield) as a white foam. This was used in
5   the next step without further purification.
<u>1-[3',5'-O-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-
α-L-arabinofuranosyl]-uracil (11)</u>
        To a stirred suspension of 10 (7.4 g, 30.3 mmol)
in pyridine was added 1,3-dichloro-1,1,3,3-
10   tetraisopropyldisiloxane (12.74 ml, 36.36 mmol). This
was stirred at room temperature until the reaction was
complete (5 hours). The solvent was evaporated to a
residue which was dissolved in EtOAc (500 ml) and
washed successively with H_2O, 5% HCl, H_2O, saturated
15      $NaHCO_3$, and brine. After drying the EtOAc portion over
Na_2SO_4, the solution was filtered and evaporated to
give the crude product 11 which was used in the next
step without further purification.
<u>1-[2'-O-Phenoxythiocarbonyl-3',5'-O-(1,1,3,3-
20   tetraisopropyldisiloxane-1,3-diyl)-α-
L-arabinofuranosyl]-uracil (12)</u>
        To a solution of 11 (30.3 mmol) in anhydrous MeCN
were added 4-dimethylaminopyridine (DMAP) (7.2 g, 58.78
mmol), and phenylchlorothionoformate (4.7 ml, 33.33
25   mmol). The solution was stirred at room temperature
for 24 hours. Then, the solvent was evaporated to a
residue which was dissolved in EtOAc (750 ml) and
washed successively with H_2O, 5% HCl, H_2O, saturated
$NaHCO_3$, and brine. After drying the EtOAc portion over
30   Na_2SO_4, the solution was filtered and evaporated to an
oil. The oil was purified on a silica gel column using
30% EtOAc/petroleum ether to produce pure 12 (13.14 g,
74.5% yield) as a white foam.
<u>NMR</u>: $(CDCl_3)\delta$ = 4.04 (m, 2H), 4.38 (m, 1H), 4.73 (dd,
35   1H), 5.79 (dd, 1H), 5.93 (d, 1H), 6.31 (dd, 1H), 7.08-
7.33 (m, 6H), 9.2 (br s, 1H).

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3',5'-O-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-α-
L-2'-deoxyuridine (13)

To a mixture of 12 (13.14 g, 21.09 mmol), in dry
toluene (300 ml) was added AIBN (0.69 g, 4.2 mmol)
followed by Bu₃SnH (28.4 ml, 105.4 mmol). The solution
was deoxygenated with argon and heated at 75°C for four
hours. The solvent was then evaporated and the residue
was purified on a silica gel column using 30%
EtOAc/petroleum ether to give pure 13 (9.29 g, 88.4%
yield) as a white foam.
NMR: (CDCl₃) δ = 2.15 (2 t, 1H), 2.81 (m, 1H), 3.82
(dd, 1H), 4.05 (m, 2H), 4.56 (q, 1H), 5.75 (dd, 1H),
6.15 (t, 1H), 7.69 (d, 1H), 9.38 (br s, 1H).

2'-Deoxy-α-L-uridine (14)

A mixture of compound 13 (9.2 g, 18.63 mmol) and
NH₄F (6.9 g, 186.3 mmol) in MeOH (200 ml) was stirred
in an oil bath at 60°C for 3 hours. Silica gel (5 g.)
was added and the mixture was evaporated to a dry
powder. This powder was added to a silica column and
eluted with 10-15% MeOH/CHCl₃ to produce pure 14 (3.70
g, 83% yield) as a white foam.
NMR: (DMSO-d₆) δ = 1.87 (m, 1H), 2.56 (m, 1H), 3.41
(m, 2H), 4.15 (m, 1H), 4.22 (m, 1H), 4.44 (t, 1H), 4.92
(t, 1H), 5.38 (d, 1H), 5.62 (d, 1H), 6.09 (dd, 1H).

Example 3
Synthesis of 2'-deoxy-α-L-cytidine

3',5'-Di-O-benzoyl-2'-deoxy-α-L-uridine (15)

A solution of BzCN (0.61 g, 4.67 mmol) in MeCN (10
ml) was added dropwise to a suspension of compound 14
(0.43 g, 1.87 mmol) in MeCN (10 ml) followed by Et₃N
(0.1 ml). The reaction was stirred at room temperature
for three hours after which time the solvent was
evaporated to dryness. The crude material was purified
on a silica gel column using 50% EtOAc/petroleum ether
to give pure 15 (0.57 g, 70% yield) as yellow foam.

NMR: (CDCl₃) δ = 2.55 (d, 1H), 2.96 (dt, 1H); 4.56 (m, 2H), 4.86 (t, 1H), 5.61 (d, 1H), 5.72 (dd, 1H), 6.31 (dd, 1H), 7.40-7.63 (m, 7H), 7.87-8.06 (m, 4H), 8.92 (br s, 1H).

3',5'-Di-O-benzoyl-2'-deoxy-4-thio-α-L-uridine (16)

A boiling solution of compound 15 (0.54 g, 1.25 mmol) in anhydrous dioxane was treated with P₂S₅ (0.61 g, 2.75 mmol) and the mixture was refluxed under a nitrogen atmosphere for one hour. Remaining solids were filtered from the hot solution and washed on the filter with additional dioxane. The filtrate was evaporated to dryness and the crude product was purified on a silica gel column using 30% EtOAc/petroleum ether to give pure 16 (0.42 g, 74% yield) as a yellow oil.

NMR: (CDCl₃) δ = 2.59 (d, 1H), 2.93 (dt, 1H), 4.58 (m, 2H), 4.89 (t, 1H), 5.63 (d, 1H), 6.26 (dd, 1H), 6.4? (dd, 1H), 7.40-8.10 (m, 11H), 9.54 (br s, 1H).

2'-Deoxy-α-L-cytidine (17)

Compound 16 (0.42 g, 9.28 mmol) was treated with NH₃/MeOH (50 ml) in a steel bomb at 100°C for 10 hours. After cooling, the solvent was evaporated to dryness, the residue was dissolved in water (50 ml) and washed with ether (3 x 50 ml). The water layer was treated with charcoal, filtered through Celite and evaporated to dryness by coevaporation with EtOH. The semi-solid obtained was crystallized from EtOH/ether to give compound 17 (0.18 g, 85.7% yield).

NMR: (DMSO-d₆) δ = 1.66 (d, H), 2.50 (m, 1H), 3.40 (m, 1H), 4.12 (m, 1H), 4.15 (m, 1H), 4.86 (t, 1H), 5.21 (d, 1H), 5.69 (d, 1H), 6.03 (dd, 1H), 7.02 (br d, 1H), 7.74 (d, 1H).

N⁴-benzoyl-2'-deoxy-α-L-cytidine (18)

To a stirring suspension of compound 17 (0.82 g, 3.61 mmol) in pyridine (50 ml) chilled in an ice bath ClSiMe₃ (2.3 ml, 18.05 mmol) was added dropwise over 30 minutes. BzCl (2.1 ml, 18.05 mmol) was then added

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dropwise and the reaction mixture was cooled at room
temperature for two hours. The reaction mixture was
again cooled in an ice bath and cold water (10 ml) was
added dropwise. Fifteen minutes later, concentrated
5   NH₄OH (10 ml) was added to produce a solution ammonia
concentration of about 2M. Thirty minutes after the
addition of the ammonia solution, the solvent was
evaporated, dissolved in water and washed with ether.
Evaporation of this aqueous solution provided the crude
10   product (18) which was used in the next step without
further purification.

N⁴-Benzoyl-5'-O-(di-p-methoxytrityl)-2'-c-L-cytidine
(19)

To a solution of compound 18 in dry pyridine was
15   added 4.4'-dimeththoxytrityl chloride (1.34 g, 3.96
mmol), DMAP (0.888 g, 0.72 mmol), and triethylamine
(0.8 ml, 5.54 mmol). The reaction mixture was stirred
at room temperature overnight. The EtOAc solution was
washed with water, saturated NaHCO₃ and brine. The
20   solution was then dried over Na₂SO₄, filtered and
evaporated to dryness. The crude material was purified
on a silica gel column using 5% MeOH/CHCL₃ to produce
pure 19 (1.08 g, 47% yield). Some of the starting
material, 18, was recovered and recycled.

25   NMR: (CDCl₃ β - 2.60 (d, 1H), 2.82 (m, 1H), 3.18 (dd,
1H), 3.30 (dd, 1H), 3.80 (s, 1H), 4.50 (d, 1H), 4.55
(t, 1H), 6.18 (d, 1H), 6.82 (d, 4H), 7.20-7.65 (m, 14),
7.90 (d, 1H), 8.12 (d, 1H). Rf - 0.46 in 10%
MeOH/CHCl₃.

30   This compound was then redissolved in pyridine
(10 ml). Acetic anhydride (2 ml) was added and the
mixture was stirred at room temperature for 3.5 hours.
The pyridine was removed in vacuo and the residue was
partitioned between EtOAc and 0.1 N HCl. Then the
35   organic layer was washed successively with saturated
NaHCO⁻ and brine. The EtOAc solution was dried over
Na₂SO₄ and evaporated to a colorless foam (754 mg).

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NMR: (DMSO-d₆ β = 1.95 (s, 3H), 2.36 (m, 1H), 3.75-
3.85 (m, 2H), 4.03 (m, 1H), 4.45 (m, 1H), 6.26 (t, 1h),
8.05 (d, 1H).

Example 4
Synthesis of Dimers

5   The dimers were prepared from the monomeric
materials by the general scheme shown in Scheme 2.

A.   α-L, β-D 5 FUdP Dimer (L-103)
5'-O-Dimethoxytrityl-α-L-5-fluoro-2'-deoxyuridine (20a)

10   α-L-5-fluoro-2'-deoxyuridine (19a) was dissolved
in 10 ml of dry, distilled pyridine. To this solution
was added 4,4'-dimethoxytrityl chloride (813 mg, 2.4
mmol) and 4-dimethylaminopyridine (DMAP) (50 mg, 0.4
mmol). The mixture was stirred under an argon

15   atmosphere for 16 hours. After this time, the pyridine
was stripped off in vacuo. The residue was dissolved
in dichloromethane (50 ml). The organic layer was
washed with .03N HCl, brine, saturated NaHCO₃, water
and again with brine. The organic layer was dried over

20   Na₂SO₄, filtered and evaporated in vacuo to a residue
which was purified on a silica gel column using 10%
MeOH/CHCl₃. Pure fractions were pooled and evaporated
to give the pure product as an off-white foam (679 mg,
86% yield). Rf = 0.48 in 10% MeOH/CHCl₃.

25   NMR: (DMSO-d₆) δ = 2.3 (dd, 1H), 2.72-2.81 (m, 1H),
3.15-3.26 (m, 2H), 3.75 (s, 6H), 4.45 (m, 2H), 6.23
(dd, 1H), 6.92 (d, 1H), 7.2-7.3 (m, 13 H), 7.94 (d,
1H).

5'-O-Dimethoxytrityl-α-L-5-fluoro-2'-deoxyuridine-3'-
30   N,N-diisopropylmethoxy phosphoramidite (21a)

        The 5'-O-dimethoxytrityl-α-L-5-fluoro-2'-
deoxyuridine (20a, 548 mg, 1 mmol) was dissolved in
anhydrous dichloromethane (20 ml). N,N-
diisopropylethylamine (518 mg, 700, μl) was added

35   through a septum, followed by chloro-N,N-

diiscpropylmethoxyphosphine (297 mg), under an argon
atmosphere. The reaction was stirred for 30 minutes.
The solvent was evaporated and the residue was
partitioned between an 80% EtOAc/triethylamine mixture

5   and brine. The organic layer was washed with 0.1 N
HCl, saturated NaHCO₃ solution and brine. The organic
residue was evaporated to dryness and the residue was
purified on a silica gel column using a mixture of
dichloromethane. EtOAc and triethylamine (45:45:10;Rf =

10   0.69). The product (390 mg) was isolated as a yellow
foam and it was used in the next step without further
purification.

<u>3'-O-Acetoxy 5'-dimethoxytrityl β-D-5-fluoro-2'-</u>
<u>deoxyuridine (23b)</u>

15   β-D-5-fluoro-2'-deoxyuridine (22b, 432 mg, 2 mmol)
was dissolved in 10 ml of dry, distilled pyridine. To
this solution was added 4,4'-dimethoxytrityl chloride
(813 mg, 2.4 mmol) and DMAP (50 mg, 0.4 mmol). The
mixture was stirred under an argon atmosphere for 16

20   hours. After this time, the pyridine was stripped off
in vacuo. The residue was dissolved in dichloromethane
(50 ml). The organic layer was washed with 0.3 N HCl,
brine, saturated NaHCO₃, and brine. The organic layer
was dried over Na₂SO₄, filtered and evaporated in vacuo

25   to a residue which was purified on a silica gel column,
using 10% MeOH/CHCl₃. Pure fractions were pooled and
evaporated to give the pure product as an off-white
foam (694 mg, 88% yield). Rf = 0.46 in 10%
MeOH/CHCl₃.

30   This compound was then redissolved in pyridine
(10). Acetic anhydride (2 ml) was added and the
mixture was stirred at room temperature for 3.5 hours.
The pyridine was removed in vacuo and the residue was
partitioned between EtOAc and 0.1 N HCl. Then the

35   organic layer was washed successively with saturated
NaHCO₃ and brine. The EtOAc solution was dried over
Na₂SO₄ and evaporated to a colorless foam (754 mg).

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NMR: (DMSO-d$_6$) δ = 1.95 (s, 3H), 2.36 (m, 1H), 3.75-
3.85 (m, 3H), 4.08 (m, 1H), 4.45 (m, 1H), 6.26 (t, 1H),
8.05 (d, 1H).

5'-O-Dimethoxytrityl-3'-[O-(3'-O-acetyl)-β-D-5-fluoro-
5   2'-deoxyuridinyl]-α-L-5-fluoro-2'-deoxyuridine methyl
phosphnite ester (25a)

The 3'-acetyl-β-D-5-fluoro-2'-deoxyuridine (355
mg, 0.62 mmol) was dissolved in dry acetonitrile (5
ml). Sublimed 1H-tetrazole (80 mg) was added and the
10   mixture was stirred under an argon atmosphere for 15
minutes. The solution of 21a (380 mg, 0.6 mmol),
dissolved in 5 ml of dry acetonitrile was added via
syringe to the reaction solution over 5 minutes. The
mixture was allowed to stir at room temperature for
15   three hours. The acetonitrile was evaporated *in vacuo*
to a residue. This residue was triturated with a 70%
EtOAc/ether mixture. The undissolved tetrazole was
filtered off and the filtrate was evaporated to give a
dry yellow foam (468 mg). This foam was used in the
20   next step without further purification.

(3'-Acetoxy-β-D-5-fluoro-2'-deoxyuridinyl)-α-L-5-
fluoro-2'-deoxyuridine methyl phosphate ester (26a)

The dimer, 25a (504 mg), was dissolved in 8 ml of
THF and 2 ml of 2,6 lutidine containing 0.2 ml of
25   water. Iodine crystals (26 mg) were added and the
contents of the loosely stoppered flask were allowed to
stir for 2.5 hours. Excess iodine was discharged by
the addition of one or two drops of saturated sodium
thiosulfate. The reaction mixture was then evaporated
30   to dryness. The residue (530 mg) was dissolved in 10
ml of 80% acetic acid/water solution and was stirred
for three hours. The solvent was evaporated and the
residue was purified on a silica gel column, using 20%
MeOH/CHCl$_3$. Fractions containing one spot by TLC (10%
35   MeOH/CHCl$_3$ Rf=0.35) were pooled and evaporated to give
the pure product (316 mg).

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NMR: (DMSO-d$_6$) δ = 1.96 (s, 3H), 2.2-2.4 (m, 2H),
2.65-2.72 (m, 1H), 3.54-3.85 (m, 4H), 4.02 (m, 1H),
4.45 (m, 2H), 6.08 (dd, 1H), 6.26 (dt, 1H), 6.05 (d,
1H), 8.08 (d, 1H).

5   P^{31} **NMR**: (CD$_3$OD) δ = 0.77 (s), 1.16 (s).
        3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-α-L-5-fluoro-2'-
        deoxyuridine (27a) [α-L, β-D 5 FUdR Dimer-3'-5'-103]

        The O-protected dimer, 26a (280 mg) was treated
        with 20 ml of saturated methanolic ammonia for 16 hours
10   at room temperature. The solvent was stripped of in
        vacuo and the residue was triturated with chloroform (3
        X 20 ml). The triturate was decanted off and the
        residue was purified by silica gel chromatography,
        using 30% MeOH/CHCl$_3$. Pure fractions were evaporated
15   to dryness to give the pure product (162 mg).
        NMR: (D$_2$O) δ = 2.2-2.4 (m, 2H), 2.65-2.71 (m, 1H),
        3.54-3.85 (m, 5H), 4.05 (t, 1H), 4.42 (m, 2H), 6.06
        (dd, 1H), 6.24 (dt, 1H), 8.04 (d, 1H), 8.06 (d, 1H).
        P^{31} NMR: (CD$_3$OD) δ = 0.04 (s).
20   5'-O-Dimethoxytrityl-β-D-5-fluoro-2'-deoxyuridine-3'-
        N,N-diisopropylmethoxy phosphoramidite (21b)

        The 5'-O-dimethoxytrityl-β-D-5-fluoro-2'-
        deoxyuridine (20a, 548 mg, 1 mmol) was dissolved in
        anhydrous dichloromethane (20 ml), N,N-
25   diisopropylethylamine (518 mg, 700 ml) was added
        through a septum, followed by chloro-N,N-
        diisopropylmethoxyphosphine (297 mg), under an argon
        atmosphere. The reaction was stirred for 30 minutes.
        The solvent was evaporated and the residue was
30   partitioned between an 80% EtOAc/triethylamine mixture
        and brine. The organic layer was washed with 0.1 N
        HCl, saturated NaHCO$_3$ solution and brine. The organic
        residue was evaporated to dryness and the residue was
        purified on a silica gel column using a mixture of
35   dichloromethane, EtOAc and triethylamine (45:45:10;
        Rf=0.62). The product (431 mg) was isolated as a

yellow foam and it was used in the next step without
further purification.

B. **β-D, α-L 5FU4R Dimer**

5'-O-Dimethoxytrityl-3'-[O-(3'-O-acetyl)-α-L-5-fluoro-
2'-deoxyuridinyl]-β-D-5-fluoro-2'-deoxyuridine methyl
phosphite ester (25b)

The 3'-O-acetyl-α-L-5-fluoro-2'-deoxyuridine, 24
(355 mg, 0.62 mmol) was dissolved in dry acetonitrile
(5 ml). Sublimed 1H-tetrazole (80 mg) was added and
the mixture was stirred under an argon atmosphere for
15 minutes. The solution of 21 (380 mg, 0.6 mmol),
dissolved in 5 ml of dry acetonitrile was added via
syringe to the reaction solution over 5 minutes. The
mixture was allowed to stir at room temperature for
three hours. The acetonitrile was evaporated in vacuo
to a residue. This residue was triturated with a 70%
EtOAc/ether mixture. The undissolved tetrazole was
filtered off and the filtrate was evaporated to give a
dry yellow foam (484 mg). This foam was used in the
next step without further purification.

(3'-Acetoxy-α-L-5-fluoro-2'-deoxyuridinyl)-β-D-5-
fluoro-2'-deoxyuridine methyl phosphate ester (26b)

The dimer in reduced form, 25b (526 mg), was
dissolved in 8 ml of THF and 2 ml of 2.6 lutidine
containing 0.2 ml of water. Iodine crystals (26 mg)
were added and the contents of the loosely stoppered
flask were allowed to stir for 2.5 hours. Excess
iodine was discharged by the addition of one or two
drops of saturated sodium thiosulfate. The reaction
mixture was then evaporated to dryness. The residue
(578 mg) was dissolved in 10 ml of 80% acetic
acid/water solution and was stirred for three hours.
The solvent was evaporated and the residue was purified
on a silica gel column, using 20% MeOH/CHCl$_3$.
Fractions containing one spot by TLC (10% MeOH/CHCl$_3$ Rf
= 0.35) were pooled and evaporated to give the pure
product (342 mg).

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NMR: (DMSO-d$_6$) δ = 1.96 (s, 3H), 2.2-2.4 (m, 2H),
2.62-2.71 (m, 1H), 3.5-3.8 (m, 4H), 4.02 (m, 1H), 4.42
(m, 2H), 6.10 (dd, 1H), 6.26 (dt, 1H), 8.00 (d, 1H),
8.04 (d, 1H).

5   3'-O-(α-L-5-fluoro-2'-deoxyuridinyl) (3'-5')-β-D-5-
fluoro-2'-deoxyuridine [β-D, α-L 5FUdR Dimer], L-102
(27b)

        The O-protected dimer, 26b (170 mg) was treated
with 20 ml of saturated methanolic ammonia for 16
10   hours at room temperature. The solvent was stripped
off in vacuo and the residue was triturated with
chloroform (3 X 20 ml). The triturate was decanted off
and the residue was purified by silica gel
chromatography, using 30% MeOH/CHCl$_3$. Pure fractions
15   were evaporated to dryness to give the pure product (89
mg).
NMR: (D$_2$O) δ = 2.2-2.4 (m, 2H), 2.65-2.71 (m, 1H),
3.54-3.85 (m, 5H), 4.05 (t, 1H), 4.42 (m, 2H), 6.06
(dd, 1H), 6.23 (dt, 1H), 8.00 (d, 1H), 8.04 (d, 1H).

20   C.   α-L 4U, β-D 5 FUdR dimer (L-107)
     5'-O-(dimethoxytrityl)-2'-deoxy-α-L-uridine (20c)
        α-L-2'-deoxyuridine (1.5 g, 6.57 mmol) was
dissolved in 25 ml of dry, distilled pyridine. To this
solution was added 4,4'-dimethoxytrityl chloride (2.9
25   g, 7.89 mmol) and 4-dimethylamino pyridine (DMAP) (160
mg, 1.31 mmol). The mixture was stirred under an argon
atmosphere for 16 hours. After this time, the pyridine
was stripped off in vacuo. The residue was dissolved
in dichloromethane (50 ml). The organic layer was
30   washed with 0.3 N Hcl, brine, saturated NaHCO$_3$, and
again with brine. The organic layer was dried over
Na$_2$SO$_4$, filtered and evaporated in vacuo to a residue
which was purified on a silica gel column using 5%
MeOH/CHCl$_3$. Pure fractions were pooled and evaporated
35   to give the pure product as an off-white foam (2.84 g,
81% yield).

NMR: (DMSO-d$_6$) δ = 2.29 (d, 1H), 2.70 (m, 2H), 3.17
(m, 2H), 3.78 (s, 6H), 4.44 (m, 2H), 5.63 (d, 1H), 6.19
(d, 1H), 6.83 (d, 4H), 7.28 (m, 9 H), 7.68 (d, 1H),
9.30 (br s, 1H).

5   5'-O-(dimethoxytrityl)-α-L-2'-deoxyuridine-3'-N,N-
     diisopropylmethoxy phosphoramidite (21c)
           The 5'-O-dimethoxytrityl-α-L-2'-deoxyuridine (2.35
     g, 4.43 mmol) was dissolved in anhydrous
     dichloromethane (50 ml). N,N-diisopropylethylamine
10   (3.1 ml, 17.72 mmol) was added through a septum,
     followed by chloro-N,N-diisopropylmethoxyphosphine (1.3
     ml, 6.64 mmol), under an argon atmosphere. The
     reaction was stirred for 30 minutes. The solvent was
     evaporated and the residue was partitioned between an
15   80% EtOAc/triethylamine mixture and brine. The organic
     layer was washed with .01 N HCl, saturated NaHCO$_3$
     solution and brine. The organic residue was evaporated
     to dryness and the residue was purified on a silica gel
     column using a mixture of dichloromethane, EtOAc and
20   triethylamine (40:50:10; Rf = 0.69). The product was
     isolated quantitatively as a yellow foam and it was
     used in the next step without further purification.
     3'-Acetoxy-5'-O-dimethoxytrityl-3'-[O-5-β-D-fluoro-2'-
     deoxyuridinyl]-2'-deoxy-α-L-uridine methyl phosphite
25   ester (23c)
           The 3'-O-acetyl-D-5-fluoro-2'-deoxyuridine (0.95
     g, 3.29 mmol) was dissolved in dry acetonitrile (125
     ml). Sublimed 1H-tetrazole (350 mg, 4.91) was added
     and the mixture was stirred under an argon atmosphere
30   for 15 minutes. The solution of 21e (4.91 mmol),
     dissolved in 5 ml of dry acetonitrile was added via
     syringe to the reaction solution over 5 minutes. The
     mixture was allowed to stir at room temperature for
     three hours. The acetonitrile was reduced in vacuo to
35   a residue. This residue was triturated with a 70%
     EtOAc/ether mixture. The undissolved tetrazole was
     filtered off and the filtrate was evaporated to give a

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dry yellow foam. This compound was further purified on
a silica gel column using 5% MeOH/CHCl₃ to give the
pure product (2.81 g, 97% yield).

<u>3'-acetoxy-β-D-5'-fluoro-2'-deoxyuridinyl)-α-L-2'-</u>

5   <u>deoxyuridine methyl phosphate ester (26c)</u>

The dimer in reduced form, 25c (2.81 g, 3.2 mmol),
was dissolved in a mixture of THF:lutidine:water
(25:6:0.6). Iodine crystals (150 mg) were added and
the contents of the loosely stoppered flask were

10   allowed to stir for 2.5 hours. Excess iodine was
discharged by the addition of a few drops of saturated
sodium thiosulfate. The reaction mixture was then
evaporated to dryness. The residue (1.48 g) was
dissolved in 25 ml of 80% acetic acid/water solution

15   and was stirred for 3 hours. The solvent was
evaporated and the residue was purified on a silica gel
column, using 10% MeOH/CHCl₃. Fractions containing one
spot by TLC (10% MeOH/CHCl₃ Rf = 0.35) were pooled and
evaporated to give the pure product (0.465 g, 25%

20   yield).

NMR: (CD₃OD) δ = 2.09 (d, 3H), 2.40 (m, 3H), 2.80 (m,
1H), 3.73 (dd, 3H), 4.30 (m, 3H), 4.63 (m, 1H), 5.05
(m, 1H), 5.23 (m, 1H), 5.70 (d, 1H), 6.13 (m, 1H), 6.20
(m, 1H), 7.73 (d, 1H), 7.82 (d, 1H).

25   P³¹ NMR: (CD₃OD) δ = 0.56 (s), 0.84 (s).

<u>3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)(3'→5')-α-L-2'-</u>
<u>deoxyuridine [L-107] (27c)</u>

The O-protected dimer, 26c (465 mg, 0.78 mmol) was
treated with 50 ml of saturated methanolic ammonia at

30   room temperature. The solvent was stripped off *in*
vacuo and the residue was triturated with chloroform (3
X 20 ml). The triturate was decanted off and the
residue was purified by silica gel chromatography,
using 30% MeOH/CHCl₃. Pure fractions were evaporated

35   to dryness to give the pure product (370 mg, 87.7%
yield).

NMR: (CD₃OD) δ = 2.23 (m, 2H), 2.29 (d; 1H), 2.73(m, 1H), 4.C (d, 2H), 4.42 (m, 1H), 4.56 (m, 1H), 4.81 (m, 1H), 5.69 (d, 1H), 6.24 (m, 2H), 7.85 (d, 1H), 8.02 (d, 1H).

5   P³¹ NMR: (CD₃OD) δ = 1.25 (s).

D.   (L-109) β-L,β-L 5FUdR Dimer
       5'-O-Dimethoxytrityl-β-L-5-fluoro-2'-deoxyuridine (20d)

       β-L-5-fluoro-2'-deoxyuridine (19d, 1.42 g, 5.77 mmol) was dissolved in 25 ml of dry, distilled
10   pyridine. To this solution was added 4,4'-dimethoxytrityl chloride (2.34 g, 6.92 mmol) and 4-dimethylamino pyridine (DMAP) (140 mg, 1.15 mmol). The mixture was stirred under an argon atmosphere for 16 hours. After this time, the pyridine was stripped off
15   in vacuo. The residue was dissolved in dichloromethane (50 ml). The organic layer was washed with 0.3 N HCl, brine, saturated NaHCO₃, and again with brine. The organic layer was dried over Na₂SO₄, filtered and evaporated in vacuo to a residue which was purified on
20   a silica gel column using 5% MeOH/CHCl₃. Pure fractions were pooled and evaporated to give the pure product as an off-white foam (2.88 g, 98.7% yield). NMR: (CDCl₃) δ = 2.25 (m, 1H), 2.50 (m, 1H), 3.50 (m, 2H), 3.80 (s, 6H), 4.08 (m, 1H), 4.58 (m, 1H), 6.30 (t,
25   1H), 6.84 (d, 4H), 7.28 (m, 9 H), 7.82 (d, 1H), 8.58 (br s, 1H).

       3'-O-Acetoxy-5'-O-dimethoxytrityl-β-D-5-fluoro-2'-deoxyuridine (23d)

       β-L-5-fluoro-2'-deoxyuridine (20d, 800 mg, 1.46
30   mmol) was dissolved in 30 ml of dry, distilled pyridine. To this solution was added 4,4'-dimethoxytrityl chloride (813 mg, 2.4 mmol) and DMAP (40 mg, 0.29 mmol). The mixture was stirred under an argon atmosphere for 16 hours. After this time, the
35   pyridine was stripped off in vacuo. The residue was dissolved in dichloromethane (50 ml). The organic layer was washed with 0.3 N HCl, saturated NaHCO₃, and

brine. The organic layer was dried over Na$_2$SO$_4$,
filtered and evaporated *in vacuo* to a residue which was
purified on a silica gel column using 10% MeOH/CHCl$_3$.
Pure fractions were pooled and evaporated to give the
5   pure product as an off-white foam (694 mg, 88% yield).
Rf = 0.46 in 10% MeOH/CHCl$_3$.

This compound was then redissolved in pyridine (10
ml). Acetic anhydride (2 ml) was added the mixture was
stirred at room temperature for 3.5 hours. The
10   pyridine was removed *in vacuo* and the residue was
partitioned between EtOAc and 0.1 N HCl. Then the
organic layer was washed successively with saturated
NaHCO$_3$ and brine. The EtOAc solution was dried over
Na$_2$SO$_4$ and evaporated to a colorless foam.

15   This foam was dissolved in 20 ml of 80% HOAc and
stirred for three hours. The solvent was evaporated *in
vacuo* and the residue was purified on a silica gel
column using 10% MeOH/CHCl$_3$ to give (340 mg. 80%
yield).

20   <u>5'-O-Dimethoxytrityl-β-L-5-fluoro-2'-deoxyuridine-3'-
N,N-diisopropylmethoxy phosphoramidite (21d)</u>

The 5'-O-dimethoxytrityl-β-L-5-fluoro-2'-
deoxyuridine (20d, 840 mg, 1.53 mmol) was dissolved in
anhydrous dichloromethane (50 ml). N,N-
25   diisopropylethylamine (1.1 ml, 6.13 mmol) was added
through a septum, followed by chloro-N,N-
diisopropylmethoxyphosphine (0.42 ml, 2.3 mmol), under
an argon atmosphere. The reaction was stirred for 30
minutes. The solvent was evaporated and the residue
30   was partitioned between an 80% EtOAc/triethylamine
mixture and brine. The organic layer was washed with
0.1 N HCl, saturated NaHCO$_3$ solution and brine. The
organic residue was evaporated to dryness and the
residue was purified on a silica gel column using a
35   mixture of dichloromethane, EtOAc and triethylamine
(45:45:10; Rf = 0.69). The product (700 mg, 65%) was

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isolated as a yellow foam and it was used in the next
step without further purification.

<u>5'-O-Dimethoxytrityl-3'-[O-(3'-O-acetyl)-β-L-5-fluoro-
2'-deoxyuridinyl]-β-L-5-fluoro-2'-deoxyuridine methyl</u>

5   <u>phosphite ester (25d)</u>

        The 3'-acetyl-β-L-5-fluoro-2'-deoxyuridine, 24d
(330 mg, 1.15 mmol) was dissolved in dry acetonitrile
(50 ml). Sublimed 1H-tetrazole (120 mg, 1.77 mmol) was
added and the mixture was stirred under an argon

10   atmosphere for 15 minutes. The solution of 21d (950
mg, 1.36 mmol), dissolved in 5 ml of dry acetonitrile
was added via syringe to the reaction solution over 5
minutes. The mixture was allowed to stir at room
temperature for three hours. The acetonitrile was

15   reduced in vacuo to a residue. This residue was
triturated with a 70% EtOAc/ether mixture. The
undissolved tetrazole was filtered off and the filtrate
was evaporated to give a dry yellow foam. This foam
was purified on a silica gel column using 5% MeOH/CHCl$_3$

20   to give the pure product (960 mg, 93% yield).
<u>NMR</u>: (CDCl$_3$) δ = 2.10 (d, 3H), 2.28 (m, 2H), 2.49 (m,
2H), 3.42 (m, 3H), 3.51 (dd, 3H), 3.76 (s, 6H), 4.07
(m, 1H), 4.55 (m, 1H), 4.87 (m, 1H), 5.23 (m, 1H), 6.30
(m, 2H), 6.84 (d, 4H), 7.30 (m, 9H), 7.82 (m, 2H).

25   <u>(3'-Acetoxy-β-D-5-fluoro-2'-deoxyuridinyl)-α-L-5-
fluoro-2'-deoxyuridine methyl phosphate ester (26d)</u>

        The dimer in reduced form, 25d (960 mg, 1.07
mmol), was dissolved in a mixture containing
THF:lutidine:water (12:3:0.3). Iodine crystals (50 mg)

30   were added and the contents of the loosely stoppered
flask were allowed to stir for 2.5 hours. Excess
iodine was discharged by the addition of one or two
drops of saturated sodium thiosulfate. The reaction
mixture was then evaporated to dryness. The residue

35   (530 mg) was dissolved in 20 ml of 80% acetic
acid/water solution and was stirred for three hours.
The solvent was evaporated and the residue was purified

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on a silica gel column, using 10% MeOH/CHCl₃.
Fractions containing one spot by TLC (10% MeOH/CHCl₃ Rf
= 0.35) were pooled and evaporated to give the pure
product (310 mg, 46% yield).

5　　NMR: (CD₃OD) δ = 2.08 (s, 3H), 2.35-2.54 (m, 4H), 3.79
(m, 2H), 3.83 (dd, 3H), 4.18 (m, 2H), 5.08 (m, 1H),
5.29 (m, 1H), 6.24 (m, 1H), 7.86 (dd, 1H), 8.19 (dd,
1H).

P³¹ NMR: (CD₃OD) δ = 0.82 (s), 1.03 (s).

10　3'-O-(β-L-5-fluoro-2'-deoxyuridinyl)-(3'-5')-β-L-5-
fluoro-2'-deoxy uridine (27d) [L-109]

　　　The O-protected dimer, 26d (300 mg, 0.49 mmol) was
treated with 50 ml of saturated methanolic ammonia for
16 hours at room temperature. The solvent was stripped
15　off in vacuo and the residue was triturated with
chloroform (3 X 20 ml). The triturate was decanted off
and the residue was purified by silica gel
chromatography, using 30% MeOH/CHCl₃. Pure fractions
were evaporated to dryness to give the pure product
20　(240 mg, 85% yield).

NMR: (CD₃OD) δ = 2.25 (m, 3H), 2.50 (m, 1H), 3.79 (d,
2H), 4.03 (m, 1H), 4.08 (m, 2H), 4.18 (m, 1H), 4.44 (m,
1H), 4.90 (m, 1H), 6.25 (t, 1H), 8.01 (d, 1H), 8.24 (d,
1H).

25　P³¹ NMR: (CD₃OD) δ = 0.18 (s).

5. **β-L, β-D-5FUdR Dimer L-110**
5'-O-Dimethoxytrityl-3'-[O-(3'-O-acetyl)-β-L-5-fluoro-
2'-deoxyuridinyl]-β-D-5-fluoro-2'-deoxyuridine methyl
phosphite ester (25e)

30　　　The 3'-O-acetyl-β-D-5-fluoro-2'-deoxyuridine (250
mg, 0.97 mmol) was dissolved in dry acetonitrile (50
ml). Sublimed 1H-tetrazole (100 mg, 1.46 mmol) was
added and the mixture was stirred under an argon
atmosphere for 15 minutes. The solution of 21a (1.02
35　g, 1.46 mmol), dissolved in 5 ml of dry acetonitrile
was added via syringe to the reaction solution over 5
minutes. The mixture was allowed to stir at room

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temperature for three hours. The acetonitrile was
reduced *in vacuo* to a residue. This residue was
triturated with a 70% EtOAc/ether mixture. The
undissolved tetrazole was filtered off and the filtrate
5   was evaporated to give a dry yellow foam. This foam
was purified on a silica gel column using 5% MeOH/CHCl₃
to give the pure product quantitatively.

(3'-Acetoxy-β-L-5-fluoro-2'-deoxyuridinyl)-β-D-5-
fluoro-2'-deoxyuridine methyl phosphate ester (26e)

10   The dimer in reduced form, 25e (700 mg, 0.78
mmol), was dissolved in a mixture containing
THF:lutidine:water (25:6:0.6). Iodine crystals (100
mg) were added and the contents of the loosely
stoppered flask were allowed to stir for 2.5 hours.
15   Excess iodine was discharged by the addition of one or
two drops of saturated sodium thiosulfate. The
reaction mixture was then evaporated to dryness. The
residue was dissolved in 25 ml of 80% acetic acid/water
solution and was stirred for three hours. The solvent
20   was evaporated and the residue was purified on a silica
gel column, using 10% MeOH/CHCl₃. Fractions containing
one spot by TLC (10% MeOH/CHCl₃ Rf = 0.35) were pooled
and evaporated to give the pure product (340 mg, 71.4%
yield).
25   NMR: (DMSO-d₆) δ = 2.06 (s, 3H), 2.37 (m, 4H), 3.45
(m, 2H), 3.65 (d, 3H), 4.20 (m, 3H), 4.95 (m, 1H), 5.30
(m, 1H), 5.96 (m, 1H), 6.15 (t, 2H), 7.99 (d, 1H), 8.16
(d, 1H), 11.90 (br s, 2H).
P³¹ NMR: (DMSO-d₆) δ = 1.93 (s), 2.01 (s).

30   3'-O-(β-L-5-fluoro-2'-deoxyuridinyl)-(3'-5')-β-D-5-
fluoro-2'-deoxyuridine (27e) [L-110]

The O-protected dimer, 26e (340 mg, 0.57 mmol) was
treated with 100 ml of saturated methanolic ammonia for
16 hours at room temperature. The solvent was stripped
35   off *in vacuo* and the residue was triturated with
chloroform (3 X 20 ml). The triturate was decanted off
and the residue was purified by silica gel

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chromatography, using 30% MeOH/CHCl₃. Pure fractions
were evaporated to dryness to give the pure product
(200 mg, 66.9% yield).

NMR: (CD₃OD) δ = 2.20 (m, 3H), 2.53 (m, 1H), 3.79 (d,

5   2H), 4.05 (m, 3H), 4.16 (m, 1H), 4.45 (m, 1H), 6.27 (t,
       2H), 8.01 (d, 1H), 8.04 (d, 1H), 8.26 (d, 1H).

F.   α-L, β-D-5FudR Dimer (3'-3') (L-122)
       5'-O-(Dimethoxytrityl)-α-L-5-fluoro-2'-deoxyuridine-3'-
       N,N-diisopropylcyanoethyl phosphoramidite (21f)

10   The 5'-O-dimethoxytrityl-α-L-5-fluoro-2'-
       deoxyuridine (1.48 g, 2.71 mmol) was dissolved in
       anhydrous dichloromethane (50 ml). N,N-
       diisopropylethylamine (1.9 ml, 10.84 mmol) was added
       through a septum, followed by 2'-cyanoethyl-N,N-

15   diisopropylchlorophosphoramidite (0.78 ml, 3.52 mmol),
       under an argon atmosphere. The reaction was stirred
       for 30 minutes. The solvent was evaporated and the
       residue was partitioned between an 80% EtOAc/
       triethylamine mixture and brine. The organic layer was

20   washed with saturated NaHCO₃ solution and brine. The
       organic residue was evaporated to dryness and the
       residue was purified on a silica gel column using a
       mixture of dichloromethane. EtOAc and triethylamine
       (45:45:10;Rf=0.7). The product was isolated

25   quantitatively as a yellow foam and it was used in the
       next step without further purification.
       5'-O-Dimethoxytrityl-3'-[O-(5'-O-dimethoxytrityl)-β-D-
       5-fluoro-2'-deoxyuridinyl]-α-L-5-fluoro-2'-deoxyuridine
       cyanoethyl phosphite ester (25f)

30   The 5'-O-dimethoxytrityl-β-D-5-fluoro-2'-
       deoxyuridine (0.44 g, 0.81 mmol) was dissolved in dry
       acetonitrile (20 ml). Sublimed 1H-tetrazole (90 mg)
       was added and the mixture was stirred under an argon
       atmosphere for 15 minutes. The solution of 21f

35   (0.51 mg, 0.67 mmol), dissolved in 10 ml of dry
       acetonitrile was added via syringe to the reaction
       solution over 5 minutes. The mixture was allowed to

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stir at room temperature for three hours. The
acetonitrile was evaporated *in vacuo* to a residue.
This residue was triturated with a 70% EtOAc/ether
mixture. The undissolved tetrazole was filtered off
and the filtrate was evaporated to give a dry yellow
foam (970 mg). This foam was used in the next step
without further purification.

(β-D-5-fluoro-2'-deoxyuridinyl)-α-L-5-fluoro-2'-
deoxyuridine cyanoethyl phosphate ester (26f)

The dimer, 25f (970 mg), was dissolved in 16 ml of
THF and 4 ml of pyridine containing 0.4 ml of water.
Iodine crystals (50 mg) were added and the contents of
the loosely stoppered flask were allowed to stir for 1
hour. Excess iodine was discharged by the addition of
few drops of saturated sodium thiosulfate. The
reaction mixture was then evaporated to dryness. The
crude product was in EtOAc washed with saturated NaHCO$_3$
solution and brine. The organic layer was dried over
Na$_2$SO$_4$, filtered and evaporated *in vacuo*. The residue
was dissolved in 20 ml of 80% acetic acid/water
solution and was stirred until the reaction was
completed. The solvent was evaporated and the residue
was purified on a silica gel column, using 10-15%
MeOH/CHCl$_3$. Fractions containing one spot by TLC (10%
MeOH/CHCl$_3$ Rf = 0.35) were pooled and evaporated to
give the pure product (330 mg).

3'-O-(β-D-5-Fluoro-2'-deoxyuridinyl)-(3'-3')-α-L-5-
fluoro-2'-deoxyuridine (27f) [L-122]

The O-protected dimer, 26f (200 mg) was treated
with 20 ml of concentrated ammonia solution until the
reaction is completed. The solvent was stripped off *in
vacuo* and the residue was purified on DEAE cellulose
ion exchange column using gradient of NH$_4$CO$_3$ buffer
from 0.02-0.2 M. Pure fractions were evaporated at
40°C in high *vacuo* to dryness to give the pure product
(79 mg).

<u>NMR</u>: (CD$_3$OD) δ = 2.45 (m, 3H), 2.69 (m, 1H), 3.67 (m, 2H), 3.75 (m, 2H), 4.13 (t, 1H), 4.65 (m, 2H), 6.19 (m, 2H), 7.98 (td 2H).

<u>P^{31} NMR</u>: (D$_2$O) δ = -1.0(s)

5 G. <u>α-L, β-L 5fu3R Dimer</u> (L-133;
<u>5'-O-Dimethoxytrityl-3'-[O-(3'-O-acetyl)-β-L-5-fluoro-</u>
<u>2'-deoxyuridinyl]-α-L-5-fluoro-2'-deoxyuridine (25g)</u>

The 3'-O-acetyl-β-D-5-fluoro-2'-deoxyuridine (0.19 g, 0.67 mmol) was dissolved in dry acetonitrile
10 (20 ml). Sublimed 1H-tetrazole (70 mg) was added and the mixture was stirred under an argon atmosphere for 15 minutes. The solution of 21f (0.51 mg, 0.67 mmol), dissolved in 10 ml of dry acetonitrile was added via syringe to the reaction solution over 5 minutes. The
15 mixture was allowed to stir at room temperature for three hours. The acetonitrile was evaporated in vacuo to a residue. This residue was triturated with a 70% EtOAc/ether mixture. The undissolved tetrazole was filtered off and the filtrate was evaporated to give a
20 dry yellow foam (611 mg). This foam was used in the next step without further purification.

<u>(3'-Acetoxy-β-L-5-fluoro-2'-deoxyuridinyl)-α-L-5-</u>
<u>fluoro-2'-deoxyuridine cyanoethyl phosphate ester (26g)</u>

The dimer, 25g (611 mg), was dissolved in 8 ml of
25 THF and 2 ml of pyridine containing 0.2 ml of water. Iodine crystals (30 mg) were added and the contents of the loosely stoppered flask were allowed to stir for 1 hour. Excess iodine was discharged by the addition of few drops of saturated sodium thiosulfate. The
30 reaction mixture was then evaporated to dryness. The crude product was in EtOAc washed with saturated NaHCO$_3$ solution and brine. The organic layer was dried over Na$_2$SO$_4$, filtered and evaporated in vacuo. The residue was dissolved in 20 ml of 80% acetic acid/water
35 solution and was stirred until the reaction was completed. The solvent was evaporated and the residue was purified on a silica gel column, using 10-15%

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MeOH/CHCl₃. Fractions containing one spot by TLC (10%
MeOH/CHCl₃ Rf=0.35) were pooled and evaporated to give
the pure product (200 mg).

3'-O-(β-L-5-Fluoro-2'-deoxyuridinyl)-(3'-5')-α-L-5-

5   fluoro-2'-deoxyuridine (27g) [α-L β-L 5FUdR Dimer, L-
119]

The O-protected dimer, 26g (200 mg) was treated
with 20 ml of concentrated ammonia solution until the
reaction is completed. The solvent was stripped off in
10   vacuo and the residue was purified on DEAE cellulose
ion exchange column using gradient of NH₄CC₃ buffer
from 0.02-0.2 M. Pure fractions were evaporated at
40°C in high vacuo to dryness to give the pure product
(134 mg).

15   NMR: (D₂O) δ = 2.30 (m, 3H), 2.71 (m, 1H), 3.65 (m,
2H), 4.03 (m, 2H), 4.08 (t, 1H), 4.47 (m, 1H), 4.68 (m,
2H), 6.13 (d, 1H), 6.24 (td, 1H), 7.89 (d, 1H), 7.95
(d, 1H).

P³¹NMR: (D₂O) δ = 0.32(s)

20   5'-O-(Dimethoxytrityl)-β-L-2'-deoxyuridine-3'-N,N-
diisopropylmethoxy phosphoramidite (21h)

The 5'-O-Dimethoxytrityl-α-L-2'-deoxyuridine
(1.0 g, 1.88 mmol) was dissolved in anhydrous
dichloromethane (50 ml). N,N-diisopropylethylamine
25   (1.31 ml, 7.55 mmol) was added through a septum,
followed by chloro-N,N-diisopropylmethoxyphosphine
(0.55 ml, 2.83 mmol), under an argon atmosphere. The
reaction was stirred for 30 minutes. The solvent was
evaporated and the residue was partitioned between an
30   80% EtOAc/triethylamine mixture and brine. The organic
layer was washed with saturated NaHCO₃ solution and
brine. The organic residue was evaporated to dryness
and the residue was purified on a silica gel column
using a mixture of dichloromethane, EtOAc and
35   triethylamine (50:40:10; Rf=0.8). The product was
isolated quantitatively as a yellow foam and it was
used in the next step without further purification.

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<u>5'-O-Dimethoxytrityl-3'-[O-(3'-O-acetyl)-β-D-5-fluoro-
2'-deoxyuridinyl]-β-L-2'-deoxyuridine methyl phosphite
ester (25h)</u>

The 3'-O-acetyl-β-D-5-fluoro-2'-deoxyuridine
(0.54 g, 1.88 mmol) was dissolved in dry acetonitrile
(50 ml). Sublimed 1H-tetrazole (200 mg) was added and
the mixture was stirred under an argon atmosphere for
15 minutes. The solution of 21b (1.88 mmol), dissolved
in 15 ml of dry acetonitrile was added via syringe to
the reaction solution over 5 minutes. The mixture was
allowed to stir at room temperature for three hours.
The acetonitrile was evaporated in vacuo to a residue.
This residue was triturated with a 70% EtOAc/ether
mixture. The undissolved tetrazole was filtered off
and the filtrate was evaporated to give a dry yellow
foam (1.08 g). This foam was used in the next step
without further purification.

<u>(3'-Acetoxy-β-D-5-fluoro-2'-deoxyuridinyl)-β-L-2'-
deoxyuridine methyl phosphate ester (26h)</u>

The dimer, 25h (1.08 g), was dissolved in 15 ml of
THF and 3 ml of pyridine containing 0.3 ml of water.
Iodine crystals (100 mg) were added and the contents of
the loosely stoppered flask were allowed to stir for 1
hour. Excess iodine was discharged by the addition of
few drops of saturated sodium thiosulfate. The
reaction mixture was then evaporated to dryness. The
crude product was in EtOAc washed with saturated NaHCO₃
solution and brine. The organic layer was dried over
Na_2SO_4, filtered and evaporated in vacuo. The residue
was dissolved in 25 ml of 80% acetic acid/water
solution and was stirred until the reaction was
completed. The solvent was evaporated and the residue
was purified on a silica gel column, using 10-15%
MeOH/CHCL₃. Fractions containing one spot by TLC (10%
MeOH/CHCL₃ Rf=0.4) were pooled and evaporated to give
the pure product (400 mg).

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3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-β-L-5-2'-
deoxyuridine (27b) (L-117)

The O-protected dimer, 26b (400 mg) was treated
with 100 ml of methanolic ammonia solution until the
reaction is completed. The solvent was stripped off *in
vacuo* and the residue was purified on DEAE cellulose
ion exchange column using gradient of NH_4CO_3 buffer
from 0.02-0.2 M. Pure fractions were evaporated at
40°C in high *vacuo* to dryness to give the pure product
(175 mg).

NMR: (D_2O) δ = 2.40 (m, 3H), 2.61 (m, 1H), 3.80
(m,2H), 4.10 (m, 2H), 4.18 (m,2H), 4.55 (m, 1H), 4.80
(m, 1H), 5.85 (d, 1H), 6.30 (q, 2H), 7.85 (d, 1H), 8.06
(d, 1H).

P^{31}NMR: (D_2O) δ = 0.20(s)

I.   β-L-dC, β-D-5FUdR Dimer (L-113)
5'-O-Dimethoxytrityl-N⁴-benzoyl-2'-deoxy-β-L-cytidine
(20i)

N⁴-benzoyl-2'-deoxy-β-L-cytidine (0.8 g, 2.42) was
dissolved in 50 ml of dry, distilled pyridine. To this
solution was added 4,4'-dimethoxytrityl chloride
(3.0 g, 8.85 mmol) and 4-dimethylamino pyridine (DMAP)
(60 mg, 0.48 mmol). The mixture was stirred under an
argon atmosphere for 16 hours. After this time, the
pyridine was stripped off *in vacuo*. The residue was
dissolved in EtOAc (100 ml). The organic layer was
washed with water, saturated $NaHCO_3$, and brine. The
organic layer was dried over Na_2SO_4, filtered and
evaporated *in vacuo* to a residue which was purified on
a silica gel column using 10% MeOH/$CHCl_3$. Pure
fractions were pooled and evaporated to give the pure
product as an off-white foam (1.49 g, (97% yield).
Rf=0.48 in 10% MeOH/$CHCl_3$.

NMR: ($CDCl_3$-d_6) δ = 2.3 (m, 1H), 2.75 (m, 1H), 3.42
(dd, 2H), 3.80 (s, 6H), 4.15 (q, 2H), 4.52 (m, 1H),
6.30 (t, 1H), 6.82 (dd, 4H), 7.2-7.6 (m, Ar), 7.85 (d,
2H), 8.32 (d, 1H), 8.76 (br s, 1H).

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5'-O-(Dimethoxytrityl)-N'-benzoyl-2'-deoxy-β-I-
cytidine-3'-N,N-diisopropylmethyl phosphoramidite (21).

The 5'-O-dimethoxytrityl-N^4-benzoyl-2'-deoxy-β-L-
cytidine (0.6 g, 0.95 mmol) was dissolved in anhydrous

5   dichloromethane (50 ml). N,N-diisopropylethylamine
(0.66 ml, 3.79 mmol) was added through a septum,
followed by chloro-N,N-diisopropylethoxyphosphine
(0.28 ml, 1.42 mmol), under an argon atmosphere. The
reaction was stirred for 30 minutes. The solvent was

10   evaporated and the residue was partitioned between an
80% EtOAc/triethylamine mixture and brine. The organic
layer was washed with saturated NaHCO$_3$ solution and
brine. The organic residue was evaporated to dryness
and the residue was purified on a silica gel column

15   using a mixture of dichloromethane, EtOAc and
triethylamine (60:30:10;Rf=0.8). The product was
isolated quantitatively as a yellow foam and it was
used in the next step without further purification.

5'-O-Dimethoxytrityl-3'-[O-(3'-O-acetyl)-β-D-5-fluoro-
20   2'-deoxyuridinyl]-N'-benzoyl-2'-deoxy-β-L-cytidine
methyl phosphite ester (25).

The 3'-O-acetyl-β-D-5-fluoro-2'-deoxyuridine
(0.23 g, 0.78 mmol) was dissolved in dry acetonitrile
(30 ml). Sublimed 1H-tetrazole (110 mg) was added and

25   the mixture was stirred under an argon atmosphere for
15 minutes. The solution of 21 (0.94 mmol), dissolved
in 15 ml of dry acetonitrile was added via syringe to
the reaction solution over 5 minutes. The mixture was
allowed to stir at room temperature for three hours.

30   The acetonitrile was evaporated in vacuo to a residue.
This residue was triturated with a 70% EtOAc/ether
mixture. The undissolved tetrazole was filtered off
and the filtrate was evaporated to give a dry yellow
foam (0.73 g). This foam was used in the next step

35   without further purification.

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(3'-Acetoxy-β-D-5-fluoro-2'-deoxyuridinyl)-N⁴-benzoyl-
2'-deoxy-β-L-cytidine methyl phosphate ester (261)

The dimer, 251 (0.73 g), was dissolved in 20 ml of
THF and 4 ml of pyridine containing 0.4 ml of water.

5   Iodine crystals (100 mg) were added and the contents of
the loosely stoppered flask were allowed to stir for 1
hour. Excess iodine was discharged by the addition of
few drops of saturated sodium thiosulfate. The
reaction mixture was then evaporated to dryness. The

10   crude product was EtOAc washed with saturated NaHCO₃
solution and brine. The organic layer was dried over
Na₂SO₄, filtered and evaporated in vacuo. The residue
was dissolved in 25 ml of 80% acetic acid/water
solution and was stirred until the reaction was

15   completed. The solvent was evaporated and the residue
was purified on a silica gel column, using 10-15%
MeOH/CHCl₃. Fractions containing one spot by TLC (10%
MeOH/CHCl₃ Rf=0.4) were pooled and evaporated to give
the pure product (108 mg).

20   3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-2'-deoxy-
β-L-cytidine (271) (L-113)

The O-protected dimer, 261 (108 mg) was treated
with 100 ml of methanolic ammonia solution until the
reaction is completed. The solvent was stripped off in

25   vacuo and the residue was purified on DEAE cellulose
ion exchange column using gradient of NH₄CO₃ buffer
from 0.02-0.2 M. Pure fractions were evaporated at
40°C in high vacuo to dryness to give the pure product
(56 mg).

30   NMR: (D₂O) δ =
P³¹NMR: (D₂O) δ = 0.05(s)
J.   β-D-5FDdR, β-L-dC Dimer (L-114)
5'-O-Dimethoxytrityl-3'-[O-(3'-O-acetyl)-N⁴-benzoyl-2'-
deoxy-β-L-cytidinyl]-β-D-5-fluoro-2'deoxyuridine

35   cyanoethyl phosphite ester (251)

The 3'-O-acetyl-β-D-5-fluoro-2'-deoxyuridine
(0.25 g, 0.67 mmol) was dissolved in dry acetonitrile

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(30 ml). Sublimed 1H-tetrazole (94 mg) was added and
the mixture was stirred under an argon atmosphere for
15 minutes. The solution of 21j (0.51 g, 0.67 mmol),
dissolved in 15 ml of dry acetonitrile was added via
syringe to the reaction solution over 5 minutes. The
mixture was allowed to stir at room temperature for
three hours. The acetonitrile was evaporated *in vacuo*
to a residue. This residue was triturated with a 70%
EtOAc/ether mixture. The undissolved tetrazole was
filtered off and the filtrate was evaporated to give a
dry yellow foam (0.49 g). This foam was used in the
next step without further purification.

(3'-acetoxy-N⁴-benzoyl-2'-deoxy-β-L-cytidinyl)-β-D-5-
fluoro-2'-deoxyuridinyl cyanoethyl phosphate ester
(26j)

The dimer, 25j (0.49 g), was dissolved in 8 ml of
THF and 2 ml of pyridine containing 0.2 ml of water.
Iodine crystals (30 mg) were added and the contents of
the loosely stoppered flask were allowed to stir for 1
hour. Excess iodine was discharged by the addition of
few drops of saturated sodium thiosulfate. The
reaction mixture was then evaporated to dryness. The
crude product was EtOAc washed with saturated NaHCO₃
solution and brine. The organic layer was dried over
Na₂SO₄, filtered and evaporated *in vacuo*. The residue
was dissolved in 20 ml of 80% acetic acid/water
solution and was stirred until the reaction was
completed. The solvent was evaporated and the residue
was purified on a silica gel column, using 10-15%
MeOH/CHCl₃. Fractions containing one spot by TLC (10%
MeOH/CHCl₃ Rf=0.4) were pooled and evaporated to give
the pure product (188 mg).

3'-O-(2'-Deoxy-β-L-cytidinyl)-(3'-5')-β-D-5-fluoro-2'-
deoxyuridine (27j) (L-114)

The O-protected dimer, 26j (188 mg) was treated
with 100 ml of concentrated ammonia solution until the
reaction is completed. The solvent was stripped off *in*

vacuo and the residue was purified on DEAE cellulose
ion exchange column using gradient of NH_4CO_3 buffer
from 0.02-0.2 M.   Pure fractions were evaporated at
40°C in high vacuo to dryness to give the pure product
5   (105 mg).

NMR: (D_2O) δ = 2.30 (m, 3H), 2.50 (m, 1H), 3.60 (m,
2H), 4.05 (m, 2H), 4.10 (m, 2H), 4.20 (m, 1H), 4.52 (m,
1H), 4.75 (m, 1H), 6.05 (d, 1H), 6.29 (q, 2H), 7.89 (d,
1H), 9.03 (d, 1H).

10   P^{31}NMR: (D_2O) δ = 0.05(s)

K.   β-D 5FUdR, α-L-dC Dimer (L-115)

5'-O-Dimethoxytrityl-3'-[O-(3'-O-acetyl)-N⁴-benzoyl)-2'-
deoxy-α-L-cytidinyl)-β-D-5-fluoro-2'-deoxyuridine
cyanoethyl phosphite ester (25k)

15   The 3'-O-acetyl-β-D-5-fluoro-2'-deoxyuridine
(0.19 g, 0.51 mmol) was dissolved in dry acetonitrile
(30 ml). Sublimed 1H-tetrazole (80 mg) was added and
the mixture was stirred under an argon atmosphere for
15 minutes. The solution of 21k (0.45 g, 0.61 mmol),
20   dissolved in 15 ml of dry acetonitrile was added via
syringe to the reaction solution over 5 minutes. The
mixture was allowed to stir at room temperature for
three hours. The acetonitrile was evaporated in vacuo
to a residue. This residue was triturated with a 70%
25   EtOAc/ether mixture. The undissolved tetrazole was
filtered off and the filtrate was evaporated to give a
dry yellow foam (0.42 g). This foam was used in the
next step without further purification.

(3'-Acetoxy-N⁴-benzoyl-2'-deoxy-α-L-cytidinyl)-β-D-5-
30   fluoro-2'-deoxyuridinyl cyanoethyl phosphate ester
(26k)

         The dimer, 25k (0.42 g), was dissolved in 10 ml of
THF and 2 ml of pyridine containing 0.2 ml of water.
Iodine crystals (45 mg) were added and the contents of
35   the loosely stoppered flask were allowed to stir for 1
hour. Excess iodine was discharged by the addition of
few drops of saturated sodium thiosulfate. The

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reaction mixture was then evaporated to dryness. The
crude product was EtOAc washed with saturated NaHCO₃
solution and brine. The organic layer was dried over
Na₂SO₄, filtered and evaporated in vacuo. The residue

5   was dissolved in 25 ml of 80% acetic acid/water
solution and was stirred until the reaction was
completed. The solvent was evaporated and the residue
was purified on a silica gel column, using 10-15%
MeOH/CHCl₃. Fractions containing one spot by TLC (10%

10   MeOH/CHCl₃ Rf=0.4) were pooled and evaporated to give
the pure product (125 mg).

3'-O-(2'-deoxy-α-L-cytidinyl)-3'→5'-β-D-5-fluoro-2'-
deoxyuridine (27k)

The C-protected dimer, 26k (125 mg) was treated

15   with 100 ml of concentrated ammonia solution until the
reaction is completed. The solvent was stripped off in
vacuo and the residue was purified on DEAE cellulose
ion exchange column using gradient of NH₄CO₃ buffer
from 0.02-0.2 M. Pure fractions were evaporated at

20   40°C in high vacuo to dryness to give the pure product
(40 mg).

NMR: (D₂O) δ = 2.15 (m, 1H), 2.35 (m, 1H), 2.60 (m,
1H), 2.71 (m, 1H), 3.81 (m, 2H), 3.97 (m, 2H), 4.22 (m,
1H), 4.52 (m, 2H), 6.02 (d, 1H), 6.15 (dd, 1H), 6.28

25   (t, 1H), 7.87 (d, 1H), 8.03 (d, 1H).

P³¹NMR: (D₂O) δ = -0.12(s)

Example 5

Dimers Testing in vitro in B16 Melanoma and
P388 Leukemia and in Inhibition Assays Against

30   293 Processive Telomerase

The biological effects of the dimers were compared
with those of the monomeric 5-FUdR on P388 leukemia and
B16 melanoma cell lines and in inhibition assays
against 293 processive telomerase. Telomerase is a

35   DNA-processive enzyme that is not expressed in normal
somatic cells but generally only in germ-line cells and
fetal cells. In many types of cancer cells, enzyme

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activity is reactivated, and others, telomerase
inhibitors can therefore serve as a valuable new class
of antineoplastic agents. The results are shown in
Table 2.

5   Table 2 - Inhibition of Tumor Cell Growth and
               Telomerase Activity by 5-FUdR Dinucleoside
               Monophosphates

Compound	Growth Inhibition IC_{50} (nM)		Telomerase Inhibition (Mean±SEM) % at 1 mN
	P389	B16	
β-D FUDR	2.8	28	0
α-L, β-D Dimer	0.57	2.45	84±11
α-L FUDR	NT	389,500	NT

NT = Not Tested

        The results indicate that the prototype dimers
15   inhibit the growth of murine-cultured leukemic P388 and
      melanoma B16 cells with great potency (some IC_{50} values
      of less than 1 nM.) The IC_{50} values are several times
      more potent than FUdR. These results are unexpected
      and thus these compounds are truly unique.
20   The preliminary results of the telomerase
      inhibition are also intriguing. The α-L, β-D dimer
      inhibited the enzyme by 84% compared to control.
          These data indicate that dimers containing an
      L-sugar have extremely interesting biological profiles
25   and represent a novel class of potent antineoplastic
      agents. The activity profile of the L-dimers is
      different from that of the parent monomeric drug β-D-
      5FUdR.
          The biological effects of the dimers were compared
30   with those of the monomeric 5-FUdR on P388 leukemia and
      B16 melanoma cell lines. The results are shown in
      Table 3.

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Table 3 - *In Vitro* Testing Data

CODE #	COMPOUND	IC50 (nM)		
		L1210	P388	B16
L-101	β-D-FUdR, β-D-FUdR	0.45	0.52	2.6
L-102	β-D-FUdR, α-L-FUdR	0.71	---	3.0
L-103	α-L-FUdR, β-D-FUdR	0.41	0.57	2.45
L-107	α-L-dU, β-D-FUdR	NT	1.2	18.0
L-108	α-L-FUdR, α-L-FUdR	NT	22,200	52,200
L-109	β-L-FUdR, β-L-FUdR	NT	5860	45,900
L-110	β-L-FUdR, β-D-FUdR	NT	2.0	6.3
L-111	α-L-dC, β-D-FUdR	NT	0.7	5.0
L-112	α-L-FUdR, β-D-FUdR (5',5')	NT	56	NT
L-113	β-L-dC, β-D-FUdR	NT	95	52
L-115	β-D-FUdR, α-L-dC	NT	125	20
L-117	β-L-dU, β-D-FUdR	NT	<90	5
L-119	α-L-FUdR, β-L-FUdR	NT	240	NT
L-122	α-L-FUdR, β-L-FUdR (3',3')	NT	175	NT
L-124	β-D-FUdR, α-L-dU	NT	1190	NT
L-126	α-L-dT, β-D-FUdR	NT	104	NT
L-128	α-L-FUdR, β-D-FUdR (phosphorothioate)	NT	90	170

These data indicate that the dinucleoside monophosphate compounds containing β-D-5FUdR in conjunction with α-L or β-L-nucleosides show superior *in vitro* activities against murine P388 leukemia and B16 melanoma cell lines, as is evidenced by lower IC_{50} values. This indicates that such nucleoside dimers may indeed be acting by mechanisms different from those of 5-FUdR or are metabolized and/or transported differently from 5-FUdR.

5-FUdR or are metabolized and/or transported
differently from 5-FUdR.

Example 6

Determination of Thymidylate Synthetase Activity And
5   Its Inhibition In Intact L1210 Leukemia Cells In Vitro

The mouse leukemia L1210 cells are harvested from
the cell culture flasks and the cell concentration is
determined. The cells are then resuspended in the
desired amount of the medium to give a stock
10   concentration 5×10^7 cells/mL. Series of the dilution
of the stock solution of the compounds to be tested are
prepared (concentrations are ranged from 10^8 M to 10^{-3}
M). The solution of the compound to be tested in the
desired concentration is pipetted into a
15   microcentrifuge tube and incubated at 37°C using a
shaking water bath. The reaction is started by
addition of $[5-^3H]-2'$-deoxycytidine (10 μL,
concentration of the stock solution - 10^{-5} M) after a
30 or 60 min. preincubation with 80 μL of the cell
20   suspension and allowed to proceed for 30 min. in a
shaking water bath at 37°C. The reaction is terminated
by adding 100 μL of the 10% charcoal in 4% $HClO_4$. The
tubes are vigorously stirred by vortexing and then
centrifuged for 10 min. in a Beckman Microfuge. The
25   radioactivity of a 100 μL of supernatant fraction from
each tube is counted in a Packard Tri-Carb (model 2450
or 3255) liquid scintillation spectrometer using a
toluene based scintillation mixture. The release of
tritium is expressed as a percentage of the total
30   amount of radioactivity added. IC_{50} values determined
from dose response curves represent the concentration
of inhibitors required for 50% inhibition of the
release of tritium. Table 4 below shows the results of
the analysis of tritium release and determination of
35   the IC_{50}.

TABLE 4

Sample Code	Inhibition of Tritium Release, IC_{50} (μM)
5FUdR	0.035
L-102	0.035
L-103	0.035
L-107	> 100
L-108	> 100
L-109	> 100
L-110	6
L-111	N/T

Example 7

In Vivo Testing of Dimers in P388 Leukemia B16 Melanoma

A.   EXPERIMENTAL

1.   P388 Leukemia

B6D2F1 mice received i.p. inocula of P388 murine leukemia cells prepared by removing ascites fluid containing P388 cells from tumored B6D2F1 mice, centrifuging the cells, and then resuspending the leukemia cells in saline. Mice received 1×10^6 P388 cells i.p. on day 0. On day 1, tumored mice were treated with the dimers or vehicle control. The route of drug administration was i.p. and the schedule selected was daily x 5. The maximum tolerated doses (MTD) was 200 mg/kg for each dimer and was determined in initial dose experiments in non-tumored mice. In the actual experiments, L-103 was given at 100 mg/kg and 50 mg/kg.

2.   B16 Melanoma

B6D2F1 mice received i.p. inocula of B16 murine melanoma brei prepared from B16 tumors growing s.c. in mice (day 0). On day 1, tumored mice were treated with the dimers or vehicle control. The route of drug administration was i.p. and the schedule selected was

-52-

daily x 5. The maximum tolerated doses (MTD) was 200
mg/kg for each dimer and was determined in initial dose
experiments in non-tumored mice. In the actual
experiments, L-103 was given at 100 mg/kg and 50 mg/kg.

5   3.   Survival Standard
            The mean survival times of all groups were
calculated, and results are expressed as mean survival
of treated mice / mean survival of control mice (T/C) x
100%. A T/C value of 150 means that the mice in the
10   treated group lived 50% longer than those of the
control group; this is sometimes referred to as the
increase in life span, or ILS value.

            In the P388 studies mice that survive for 30 days
are considered long term survivors or cures while in
15   B16, mice that survive for 60 days are considered long
term survivors or cures. The universally accepted
cut-off for activity in both models, which as been used
for years by the NCI, is T/C = 125. Conventional use
of B16 and P388 over the years has set the following
20   levels of activity: T/C < 125, no activity; T/C =
125-150, weak activity; T/C = 150-200, modest activity;
T/C = 200-300, high activity; T/C > 300, with long term
survivors; excellent, curative activity.

B.   RESULTS

25   1.   P388 Leukemia
            L-103 demonstrated modest activity in the P388
leukemia in mice at all doses tested (Table 5). L-103
gave i.p. daily x 5 at doses of 100 mg/kg and 50 mg/kg
resulted in T/C values of 149 and 144 respectively.
30   Fluorodeoxyuridine (FUdR) was used as the positive drug
control in this study; FUdR produced a T/C = 164 in the
P388 test (Table 5). All agents were well-tolerated in
this experiment; there was little or no body weight
loss and no toxic deaths were recorded.

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TABLE 5

L-103 vs. Murine P388 Leukemia

Group	n	Dose	Weight Change (Day 7)	T/C
Control	(10)	0.9% Saline	+9.1%	100
L-103	(10)	100 mg/kg	+1.5%	149
L-103	(10)	50 mg/kg	-1.6%	144
FUdR	(10)	100 mg/kg	-2.7%	164

2.   Bl6 Melanoma

L-103 demonstrated modest activity against B16 melanoma implanted in mice (Table 6). L-103 (i.p.; daily x 5) gave T/C values of 139 and 134 respectively. The positive control drug FUdR resulted in modest efficacy in the B16 test; a T/C value of 135 was obtained (Table 6). All agents were well-tolerated, with little or no weight loss; no drug-related deaths occurred.

TABLE 6

L-103 vs. Murine B16 Leukemia

Group	n	Dose	Weight Change (Day 7)	T/C
Control	(10)	0.9% Saline	+4.9%	100
L-103	(10)	100 mg/kg	+2.3%	139
L-103	(10)	50 mg/kg	+5.3%	134
FUdR	(10)	100 mg/kg	-0.5%	135

L-103 demonstrated modest activity against both the P388 and B16 experimental murine tumors at the two doses tested. L-103 was approximately as active as the

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positive control drug FUdR in the B16 test, and was
somewhat less active than FUdR in the P388 test.

From the foregoing, the significance of L-sugar-
based α- and β-enantiomeric nucleosides, nucleotides
5   and their analogues as versatile, highly effective
chemotherapeutic agents is apparent. Our results on
derivatives of 5-FUdR show that L-5-FUdR-containing
isomers are less toxic than those containing β-D-5FUdR,
perhaps because they are not phosphorylated or
10   transported as the latter. We have found that dimeric
derivatives designed and prepared from α-L-5FUdR show
very potent activity against P388 leukemia cells and
B16 melanoma cell lines, exceeding that of β-D-5FUdR.
They appear to have unusual mechanisms of action,
15   including inhibition of telomerase.

Example 8

Effectiveness of Dimers in Tumors

Table 7. Evaluation of the L-Nucleoside Dimers in Human Tumor Cell Lines

Compound Code	Colon HT-29 IC₅₀(nM)	Pancreas MiaPaCa IC₅₀(nM)	Prostate MCF-7 IC₅₀(nM)	Prostate DU145 IC₅₀(nM)	Prostate LNCap %Inhib.*	Prostate PC-3 %Inhib.*
L-102	NT	gg	NT	140	NT	NT
L-103	NT	NT	NT	NT	NT	NT
L-107	>1000	40	634	466	NT	40
L-111	>1000	38	620	450	>30	>30
L-113	50	38	NT	13C	NT	NT
L-116	9	3C2	525	330	>40	>40
L-117	18	36	540	69	>50	>40
L-125	35	500	660	210	>40	>40
L-126	35	33	550	200	>40	>40
L-133	NT	NT	NT	NT	>40	/>40
L-134	NT	NT	NT	NT	NT	NT
L-135	NT	NT	NT	NT	NT	>40
FUdR	4	20	450	160	>50	>40

NT = Not Tested

*Cells were exposed to 4 different drug concentrations:
20, 50, 75 and 100 nM. In each assay, cells were treated with drug three times
(on day 1, 2 and 3). The test was a dye assay for survival of cells using Alamo
Blue. Data are presented as % growth inhibition compared to control without drug
at 100 nM.

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All patents and publications mentioned in the
specifications are indicative of the levels of those
skilled in the art to which the invention pertains.
All patents and publications are herein incorporated by
5   reference to the same extent as if each individual
publication was specifically and individually indicated
to be incorporated by reference.

One skilled in the art readily appreciates that
the patent invention is well adapted to carry out the
10   objectives and obtain the ends and advantages mentioned
as well as those inherent therein. Dimers,
pharmaceutical compositions, treatments, methods,
procedures and techniques described herein are
presently representative of the preferred embodiments
15   and are intended to be exemplary and are not intended
as limitations of the scope. Changes therein and other
uses will occur those skilled in the art which are
encompassed within the spirit of the invention or
defined by the scope of the pending claims.

20

What is claimed is:

   1.   A compound of the formulae:
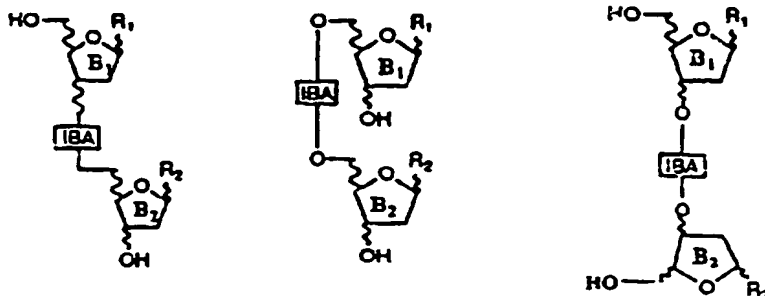
     I   II   III

    or a pharmaceutically acceptable salt thereof,

5   wherein:

    B_1 and B_2 are each selected from the group consisting of β-D, β-L and α-L nucleosides and wherein at least one of B_1 or B_2 must be β-L or α-L nucleoside.

10

    R_1 and R_2 are selected from the group of pyrimidine bases consisting of cytosine, thymine, uracil, adenine, guanine, inosine, 5 fluorouridine (5 FUdR) and other 5-halo bases; and wherein R_1

15   and R_2 can be the same or a different base or alkoxy group and wherein when B_1 or B_2 is attached to the internucleotide binding agent (IBA) at the 5' position and said B_1 or B_2 is β-L or α-L then the R_1 or R_2 attached to said base cannot be

20   cytosine; and

    IBA is selected from the group consisting of phosphodiester, phosphorothioate, methoxy phospho-triesters, methylphosphonates, phosphoro-

-55-

dithioates, phosphorothioates, silyl ethers, sulphonates and ethylenedioxy ethers.

2.   The compound of claim 1 wherein said compound is selected from the group consisting of 3'-O-(α-L-5-fluoro-2'deoxyuridinyl)-(3'→5')-β-D-5-fluoro-?'-deoxyuridine (L-102), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-α-L-5-fluoro-2'-deoxyuridine, (L-103), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-α-L-2'-deoxyuridine, (L-107), 3'-O-(α-L-5-fluoro-2'-deoxyuridinyl)-(3'→5')-α-L-5-fluoro-2'-deoxyuridine, (L-108), 3'-O-(α-L-5-fluoro-2'-deoxyuridinyl)-(3'→5')-β-L-5-fluoro-2'-deoxyuridine, (L-109), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-β-L-5-fluoro-2'-deoxyuridine, (L-110), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-α-L-2'-deoxycytidine, (L-111), 5'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(5'→5')-α-L-5-fluoro-2'-deoxyuridine (L-112), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-2'-deoxy-β-L-cytidine, (L-113), 3'-O-(2'-deoxy-β-L-cytidinyl)-(3'→5')-β-D-5-fluoro-2'-deoxyuridine (L-114), 3'-O-(2'-deoxy-α-L-cytidinyl)-(3'→5')-β-D-5-fluoro-2'-deoxyuridine (L-115), 3-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-β-L-2'-deoxyuridine (L-117), 3'-O-(β-L-2', 3'-dideoxy-cytidinyl)-(3'→5')-β-D-5-fluoro-2'-deoxyuridine (L-118), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-α-L-2', 3'-dideoxycytidine (L-120), 3'-O-(β-L-5-fluoro-2'-deoxyuridinyl)-(3'→5')-α-L-5-fluoro-2'-deoxyuridine (L-119), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→3')-α-L-5-fluoro-2'-deoxyuridine (L-122), 3'-O-(β-L-2'-deoxyuridinyl)-(3'→5')-β-D-5-fluoro-2'-deoxyuridine (L-124), 3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-α-L-2'-deoxyadenosine (L-125), 3'-O-(β-D-5-fluoro-2'-deoxyuridinly)-(3'→5')-α-L-thymidine (L-126), 3'-

-59-

O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-β-L-5-
fluoro-2'-deoxyuridine phosphorothioate (L-128),
3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-β-L-
2'-deoxyguanosine (L-133), 3'-O-(β-D-5-fluoro-2'-

5   deoxyuridinyl)-(3'→5')-α-L-2'-deoxyguanosine (L-
134), 3'-O-(β-L-5-fluoro-2'-deoxyuridinyl)-
(3'→5')-methoxy-2-deoxyribose (L-136), 3'-O-(β-D-
5-fluoro-2'-deoxyuridinyl)-(3'→5')-α-L-2'-
deoxyadenosine (L-138) and 3'-O-(β-D-5-fluoro-2'-

10   deoxyuridinyl)-(3'→5')-β-L-1-methoxy-2-deoxyribose
(L-142) or a therapeutically acceptable salt
thereof.

3.   The compound of claim 1, wherein the formulae is
       I. B_1 is β-D, B_2 is α-L, R_1 and R_2 are both 5 FUdR,
15   and IBA is a phosphodiester.

4.   The compound of claim 1, wherein the formulae is
       II, B_1 is α-L, B_2 is β-D, R_1 and R_2 are both 5-FUdR
       and INB is a phosphodiester.

5.   The compound of claim 1, wherein the compound is
20   3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-α-L-5-fluoro-
       2'-deoxyuridine, (L-103).

6.   The compound of claim 1, wherein the compound is
       3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-β-L-
       5-fluoro-2'-deoxyuridine. (L-110).

25   7.   The compound of claim 1, wherein the compound is
       3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'→5')-β-L-
       2'-deoxyuridine, (L-117).

8.   A pharmaceutical composition comprised of a
       pharmaceutically acceptable carrier and a
30   therapeutically effective amount of at least one
       compound of claim 1 or 2.

9.   A method of treating cancer in a mammal comprising
the step of administering to said mammal bearing a
cancer a therapeutically effective amount of at
least one compound of claim 1 or 2.

5   10.   A method of treating cancer in a mammal comprising
the step of administrating to said mammal bearing
a cancer, a cancer inhibiting amount of at least
one of the compounds of claim 1 or 2.

11.   A method of treating a parasitic or a viral
10   infection in a mammal comprising the step of
administrating to said mammal having the parasitic
or viral disease, a therapeutically effective
amount of at least one compound of claim 1 or 2.
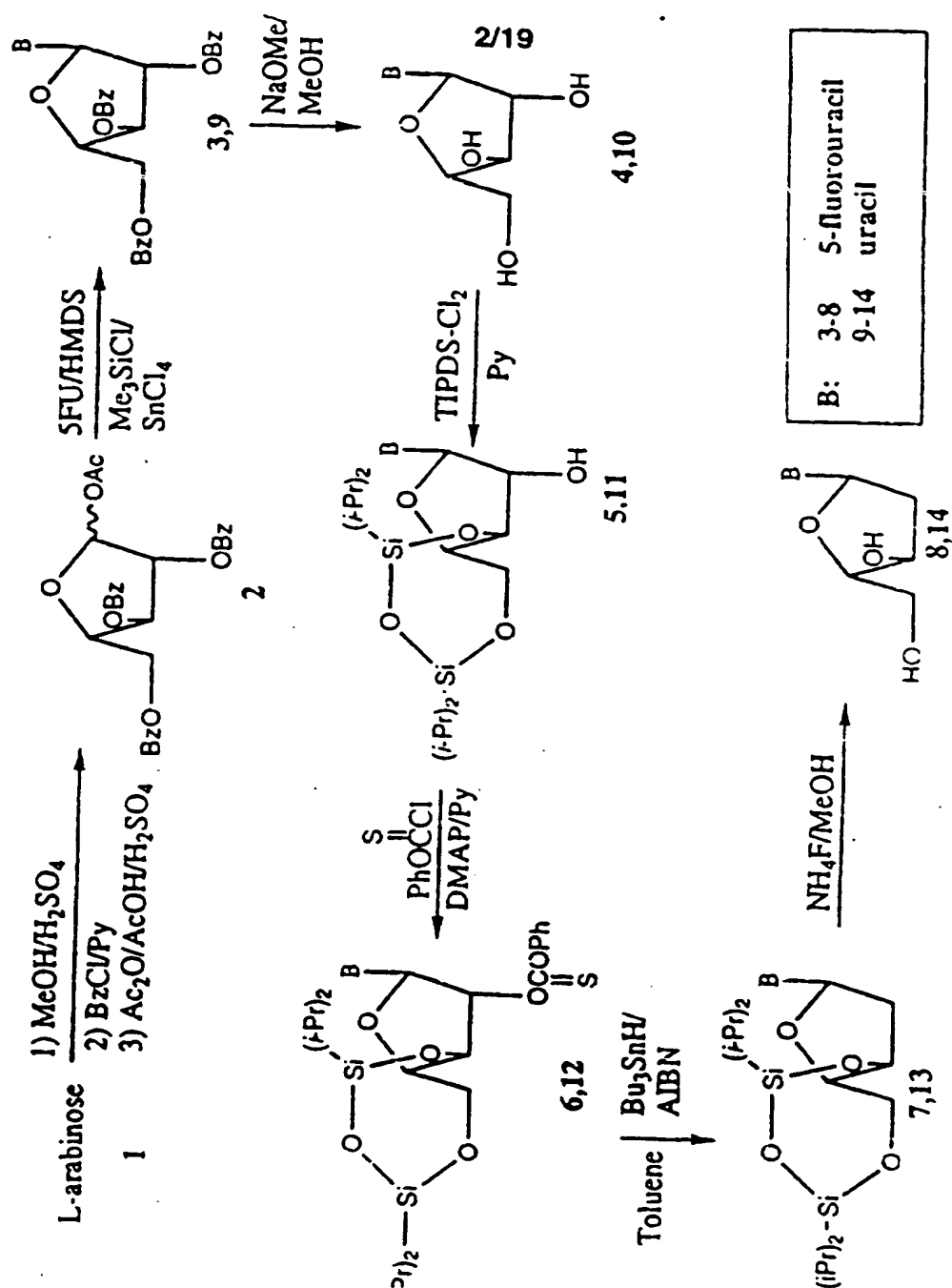
Figure 1

Figure 2A

Figure 2B

Figure 3 A & B

Figure 3C

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Series:

a R_1= α-L-5-fluorouracil, R_2=β-D-5-fluorouracil

b R_1=β-D-5-fluorouracil, R_2=α-L-5-fluorouracil

c R_1=α-L-uracil, R_2=β-D-5-fluorouracil

d R_1=β-L-5-fluorouracil, R_2=β-L-5-fluorouracil

e R_1=β-L-5-fluorouracil, R_2=β-D-5-fluorouracil

g R_1=α-L-5-fluorouracil, R_2=β-L-5-fluorouracil

h R_1=β-L-uracil, R_2=β-D-5-fluorouracil

i R_1=β-L-cytosine, R_2=β-D-5-fluorouracil

j R_1=β-D-5-fluorouracil, R_2=β-L-cytosine

k R_1=β-D=5-fluorouracil, R_2=α-L-cytosine

m R_1=α-L-adenosine R_2=β-D-5-fluorouracil

n R_1=β-D-5-fluorouracil, R_2=β-L-uracil

p R_1=α−L-thymine, R_2=β−D-5-fluorouracil

q R_1=α-L-guanine, R_2=β-D-5-fluorouracil

s R_1=β-D-1-OMe.ribose,R_2=β-L-5-fluorouracil

t R_1=β-L-1-OMe.ribose,R_2=β-D-5-fluorouracil

Figure 3 (continued)
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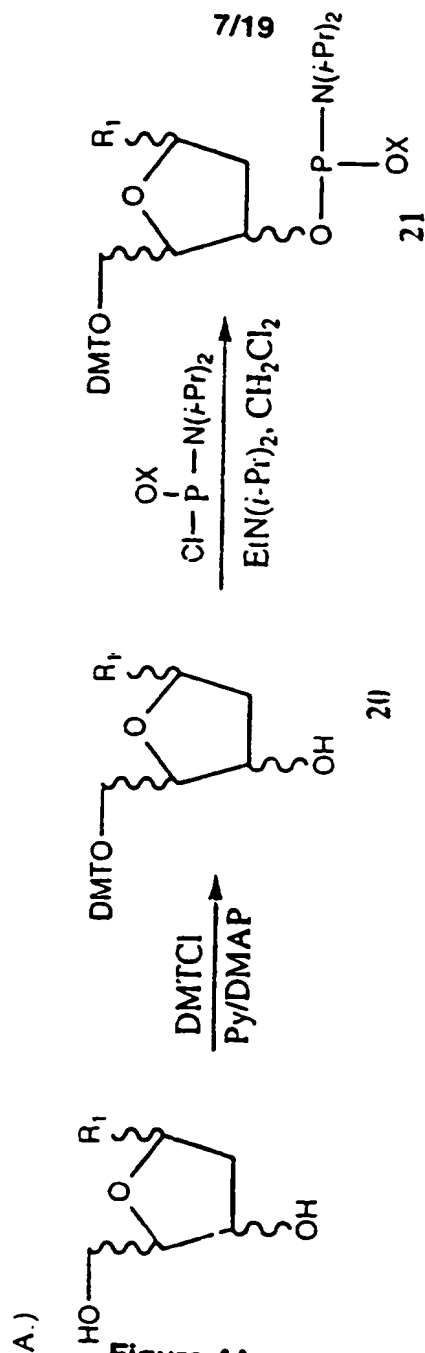
Figure 4A
SUBSTITUTE SHEET (RULE 26)
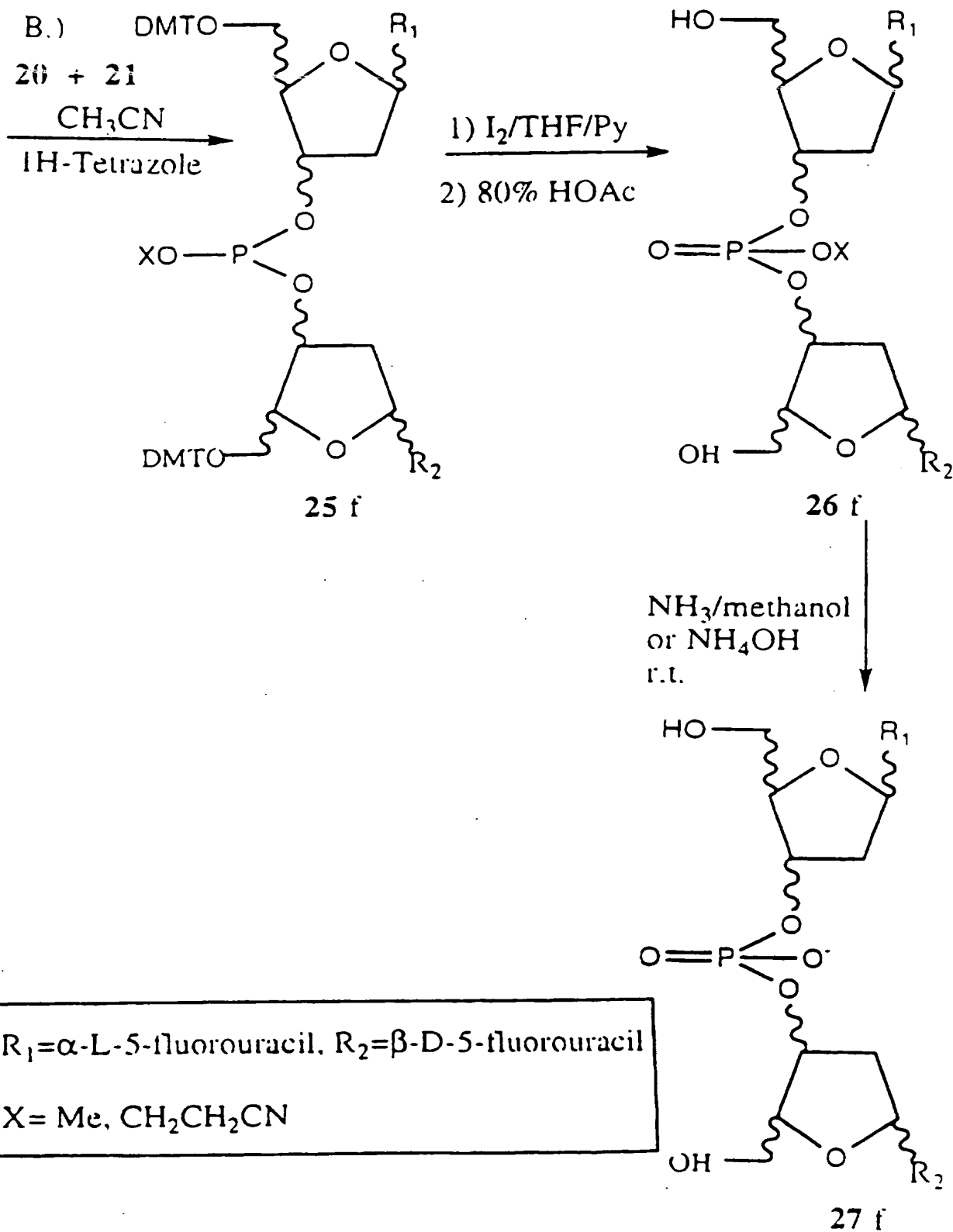
B.)

$20 + 21$

$\xrightarrow[\text{1H-Tetrazole}]{\text{CH}_3\text{CN}}$

25 f

$\xrightarrow[\text{2) 80\% HOAc}]{\text{1) I}_2/\text{THF/Py}}$

26 f

$\xrightarrow{\begin{array}{c}\text{NH}_3/\text{methanol}\\\text{or NH}_4\text{OH}\\\text{r.t.}\end{array}}$

$R_1 = \alpha\text{-L-5-fluorouracil}$, $R_2 = \beta\text{-D-5-fluorouracil}$

$X = \text{Me, CH}_2\text{CH}_2\text{CN}$

27 f

Figure 4B

Figure 5A

B.) 24 + 28

f R_1=α-L-5-fluorouracil, R_2=β-D-5-fluorouracil

X= Me, CH_2CH_2CN
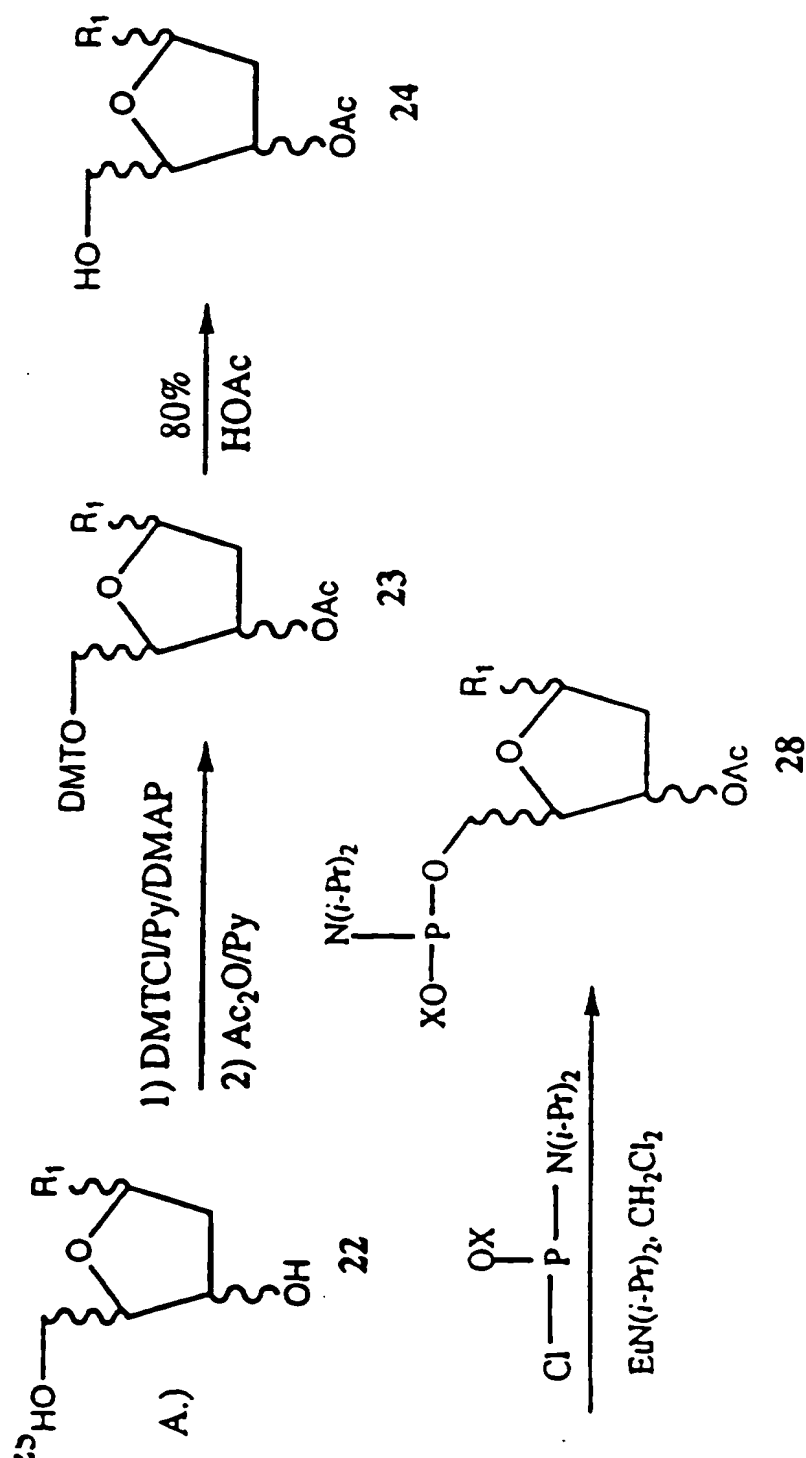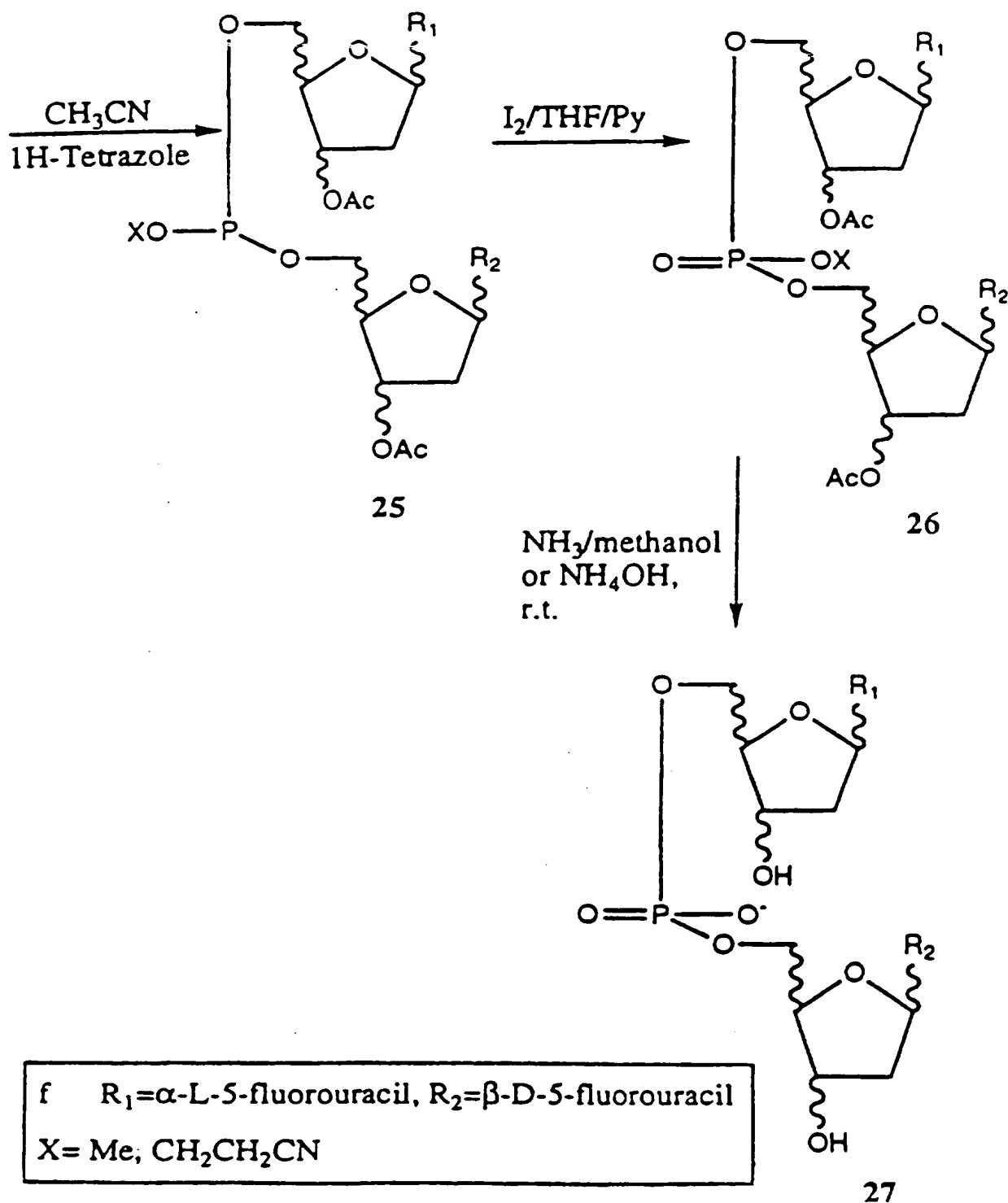
Figure 5B
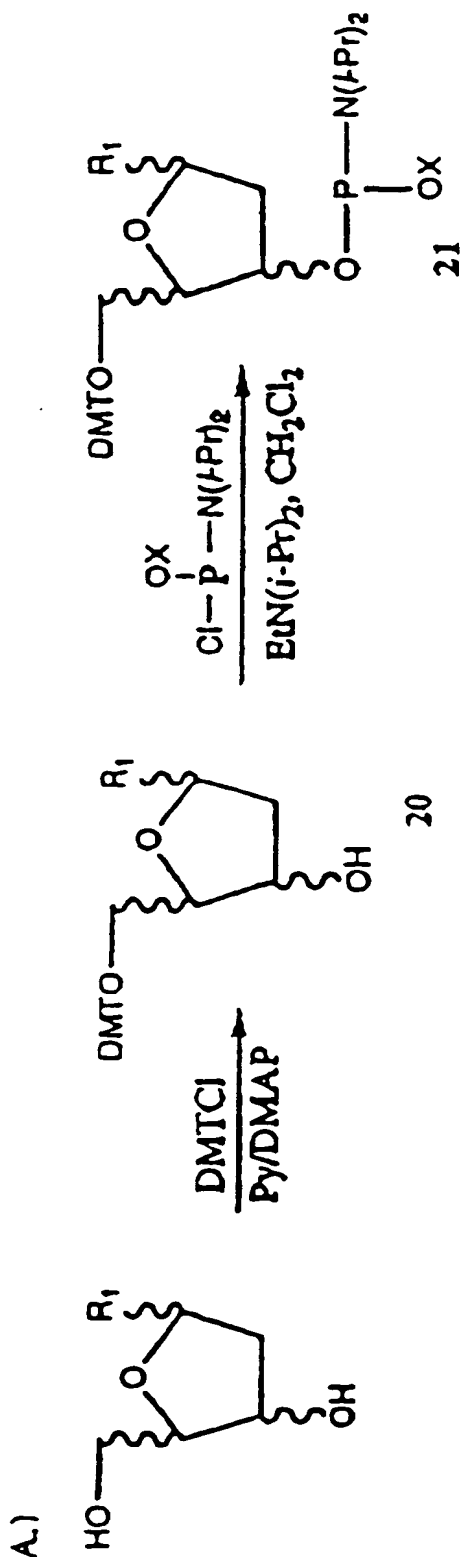
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Figure 6A

B.)

20 + 21

CH_3CN

1H-Tetrazole

1) I_2/THF/Py

2) 80% HOAc

25

26

NH_3/methanol
or NH_4OH
r.t.

f R_1=α-L-5-fluorouracil, R_2=β-D-5-fluorouracil

X= Me, CH_2CH_2CN

27

Figure 6B

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Methoxy phosphotriester

Methyl phosphonates
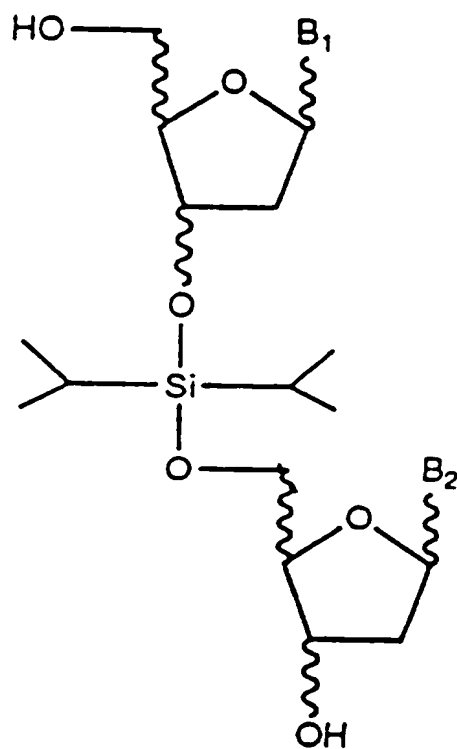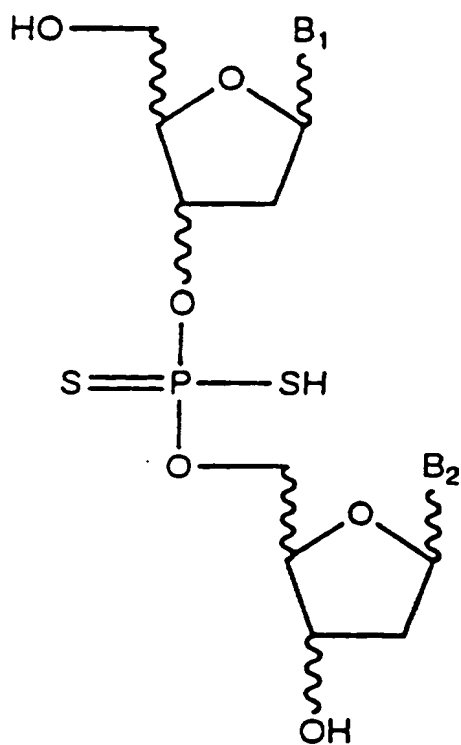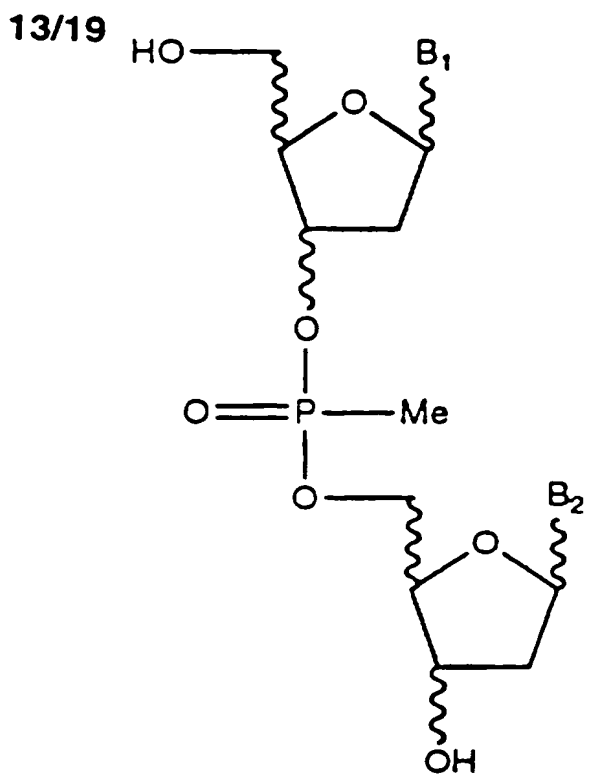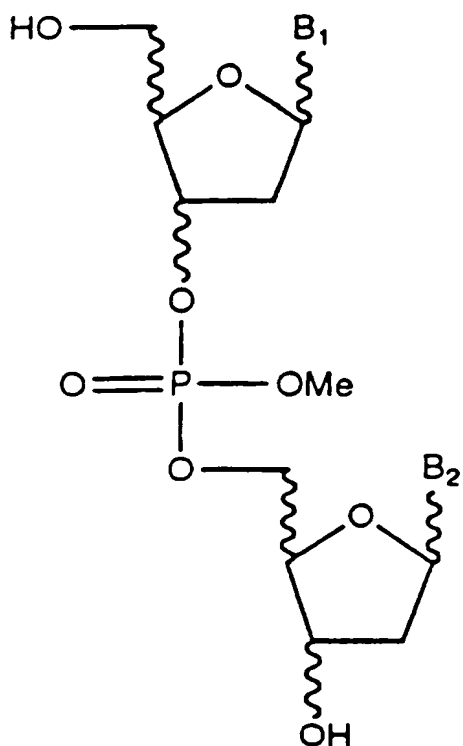
Phosphorodithioates   **Figure 7A**   Silyl Ethers
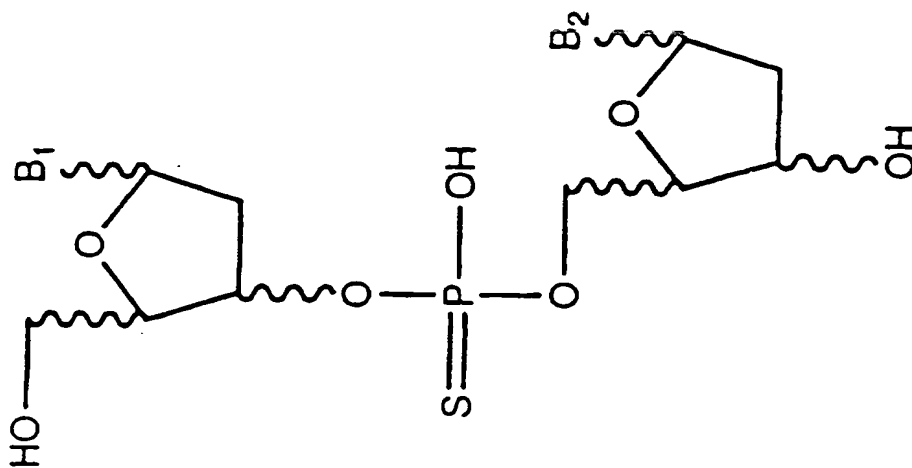
Phosphorothioates
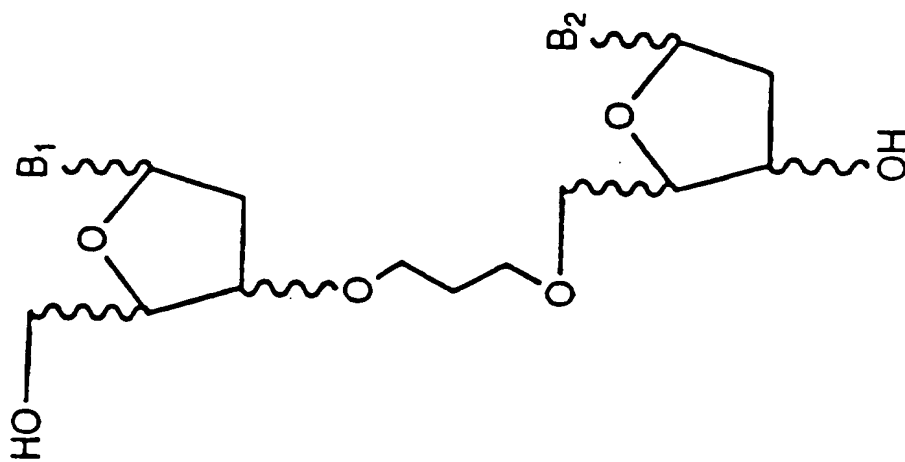
Ethylenedioxy ethers
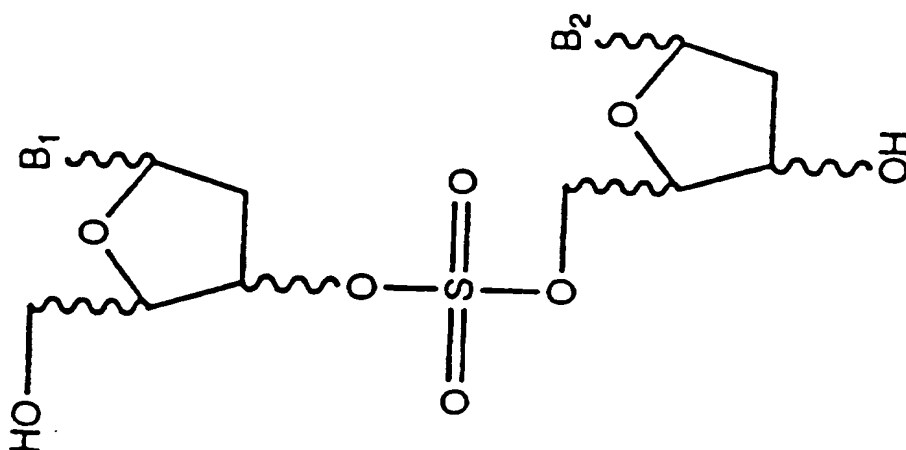
Sulfonates

Figure 7B
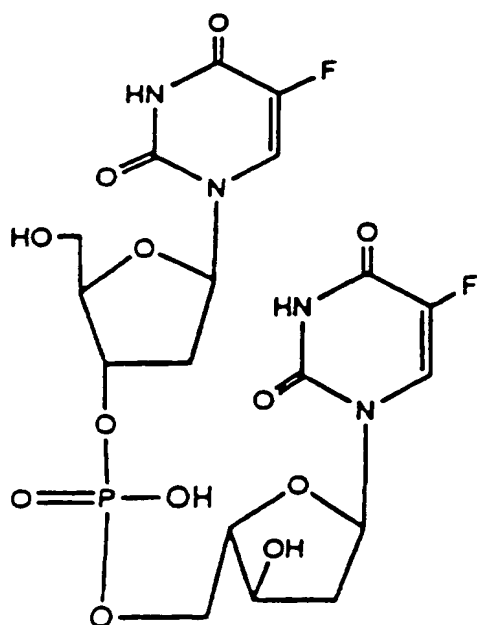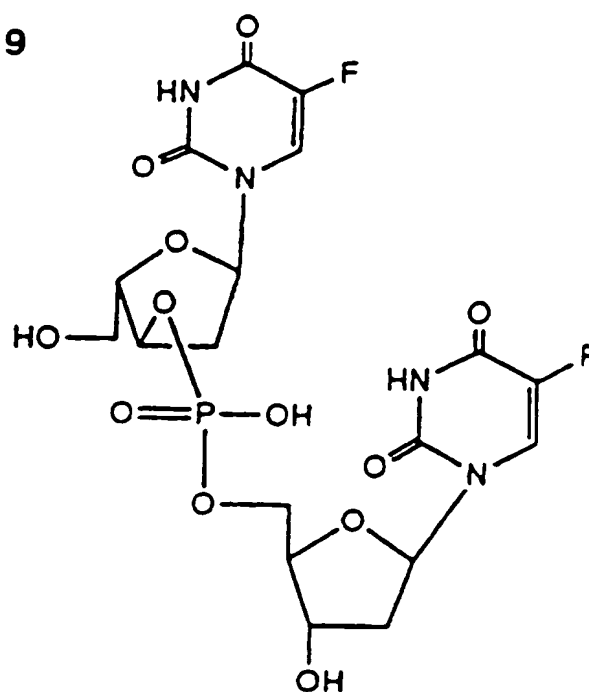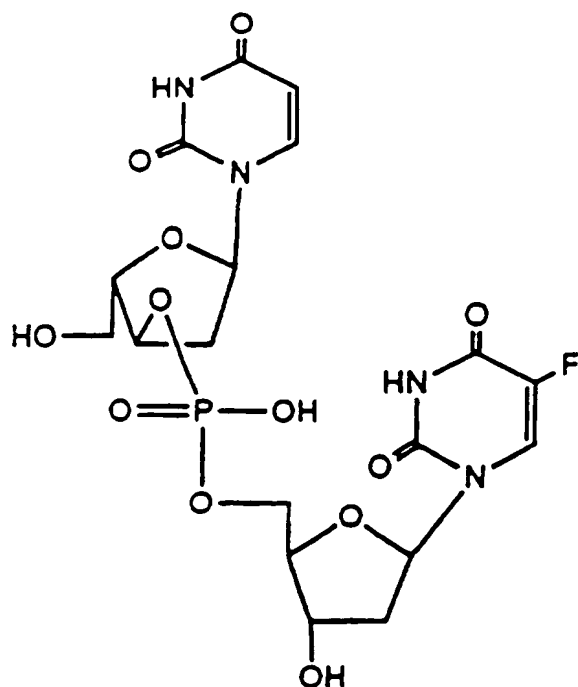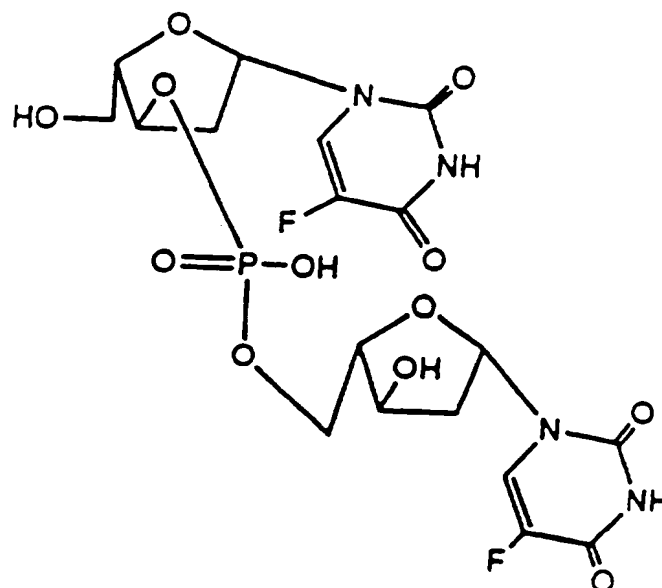
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L-102

L-103

L-107   **Figure 8A**   I -109

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L-113

L-110
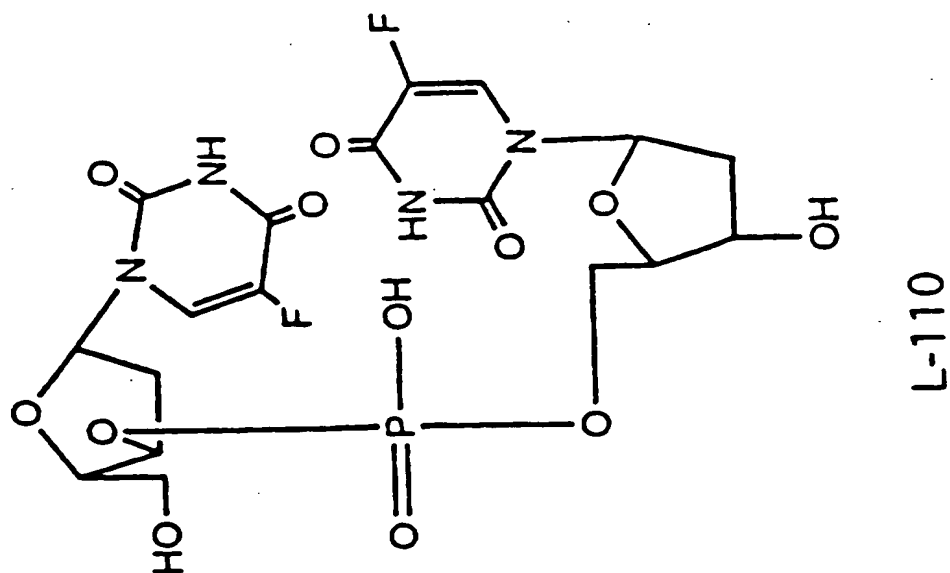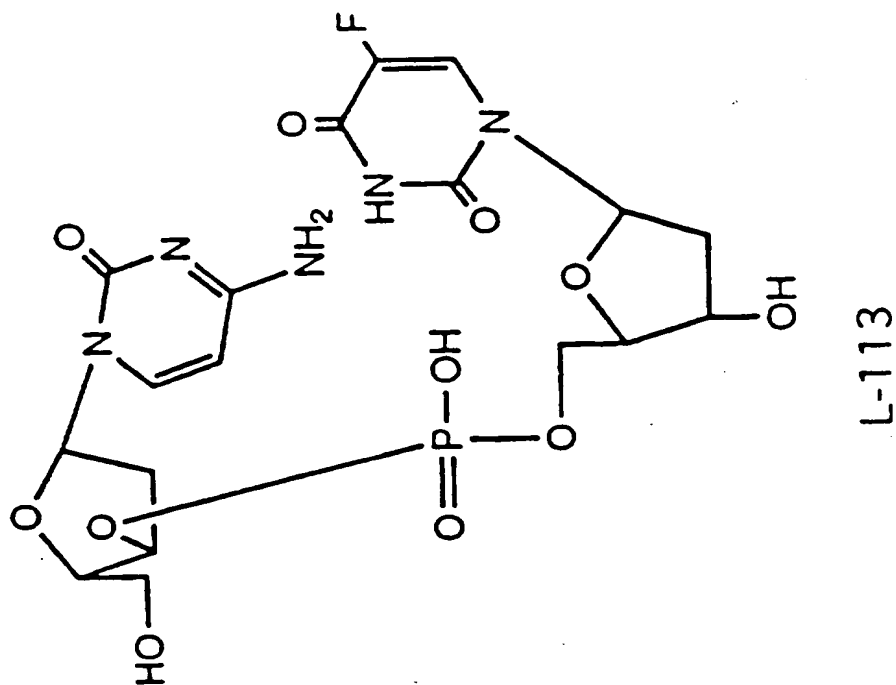
Figure 8B

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L-115

L-114

Figure 8B (continued)

L-122

L-119

L-117

Figure 8C

SUBSTITUTE SHEET (RULE 26)

L-116

L-115
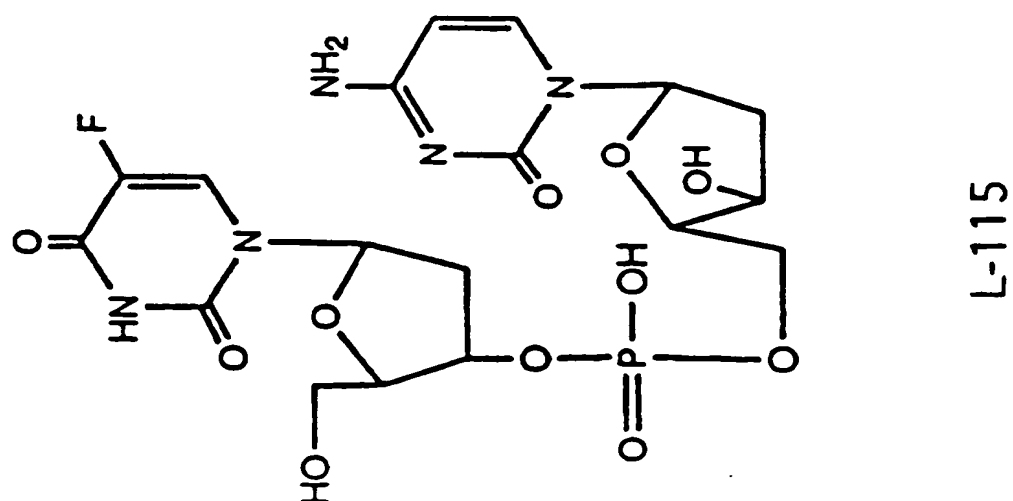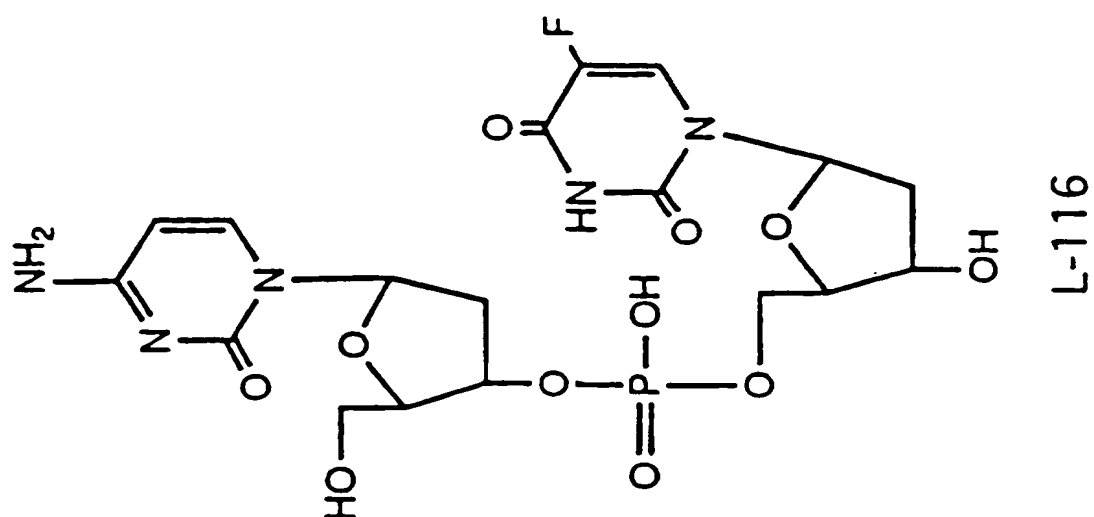
Figure 8D
SUBSTITUTE SHEET (RULE 26)

INTERNATIONAL SEARCH REPORT

A.   CLASSIFICATION OF SUBJECT MATTER
IPC(6)   :C07H 21/00, 23/00; A61K 31/76, 31/695
US CL   :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B.   FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. :   536/22.1, 23.1, 26.7, 27.6, 27.81, 28.5, 28.52, 28.54, 28.55; 514/46, 51, 63, 885

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS on line
CAS on line

C.   DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, E	US 5,559,101 A (WEIS ET AL.) 24 September 1996, see entire document.	1-11
A, E	US 5,561,120 A (LIN ET AL.) 01 October 1996, see entire document.	1-11
A, E	US 5,565,438 (CHU ET AL.) 15 October 1996, see entire document.	1-11

☐ Further documents are listed in the continuation of Box C.   ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	
"E" earlier document published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 OCTOBER 1996	**07 JAN 1997**

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INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

536/22.1, 23.1, 26.7, 27.6, 27.81, 28.5, 28.52, 28.54, 28.55; 514/46, 51, 63, 885

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